10/038,080

~~09/806,378~~

~~10/038080~~

Epperson

~~10/038,080~~

~~09/806,378~~

10/038,080

```
     FILE 'REGISTRY' ENTERED AT 15:05:27 ON 11 JUN 2003
                   E CYCLOOXYGENASE 2/CN 5
L1                 2 S E3-E4
                   E "CYCLOOXYGENASE-2"/CN 5
L2                 8 S "CYCLOOXYGENASE-2"?/CN
                   E "TAISHO NS-398"/CN 5
L3                 1 S E2
                   E FLOSULIDE/CN 5
L4                 1 S E3
                   E "MERCK MK-966"/CN 5
                   E MK 966/CN 5
L5                 1 S E3
                   E L 752/CN
L6                 1 S E5
L7                14 S L1 OR L2 OR L3 OR L4 OR L5 OR L6

L3   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS
RN   123653-11-2  REGISTRY
CN   Methanesulfonamide, N-[2-(cyclohexyloxy)-4-nitrophenyl]- (9CI)  (CA
     INDEX NAME)
OTHER NAMES:
CN   N-(2-Cyclohexyloxy-4-nitrophenyl)methanesulfonamide
CN   NS 398
CN   Taisho NS 398
FS   3D CONCORD
MF   C13 H18 N2 O5 S
CI   COM
SR   CA
LC   STN Files:   ADISINSIGHT, ADISNEWS, AGRICOLA, BIOSIS, BIOTECHNO, CA,
       CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CIN, CSCHEM, DRUGNL,
       DRUGUPDATES, EMBASE, MEDLINE, PHAR, PROMT, SYNTHLINE, TOXCENTER,
       USPATFULL
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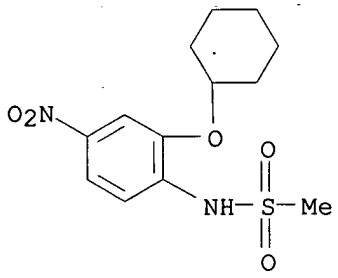


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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

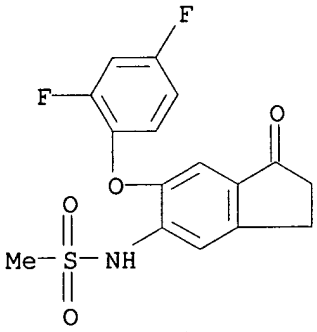
             335 REFERENCES IN FILE CA (1957 TO DATE)
               5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             336 REFERENCES IN FILE CAPLUS (1957 TO DATE)


L4   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS
RN   80937-31-1  REGISTRY
```

Searcher : Shears 308-4994

~~10/038080~~ ~~09/806,578~~ 10/638,080

CN Methanesulfonamide, N-[6-(2,4-difluorophenoxy)-2,3-dihydro-1-oxo-1H-inden-5-yl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN CGP 28238
CN **Flosulide**
CN ZK 38997
FS 3D CONCORD
MF C16 H13 F2 N O4 S
LC STN Files: ADISINSIGHT, ADISNEWS, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, DDFU, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, PHAR, SYNTHLINE, TOXCENTER, USAN, USPATFULL
(*File contains numerically searchable property data)



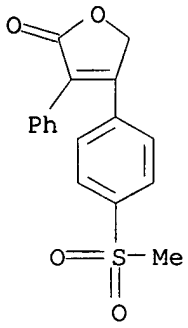
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

100 REFERENCES IN FILE CA (1957 TO DATE)
7 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
100 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 162011-90-7 REGISTRY
CN 2(5H)-Furanone, 4-[4-(methylsulfonyl)phenyl]-3-phenyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 3-Phenyl-4-[4-(Methylsulfonyl)phenyl]-2(5H)-furanone
CN MK 0966
CN **MK 966**
CN Rofecoxib
CN Vioxx
FS 3D CONCORD
DR 186912-82-3
MF C17 H14 O4 S
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN, CSCHEM, DIOGENES, DRUGNL, DRUGPAT, DRUGUPDATES, EMBASE, IPA, MRCK*, PHAR, PHARMASEARCH, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2,

Searcher : Shears 308-4994

USPATFULL
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

435 REFERENCES IN FILE CA (1957 TO DATE)
13 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
444 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L6 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 186912-76-5 REGISTRY
CN **L 752860 (9CI)** (CA INDEX NAME)
ENTE A pharmaceutical
MF Unspecified
CI MAN
SR CA
LC STN Files: ADISINSIGHT, BIOSIS, CA, CAPLUS, DRUGNL, DRUGUPDATES, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

E FLOCULIDE/CN 5
L52 1 S E3

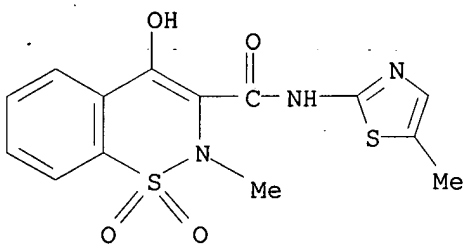
L52 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 187112-24-9 REGISTRY
CN **Floculide (9CI)** (CA INDEX NAME)
ENTE A pharmaceutical
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
3 REFERENCES IN FILE CA (1957 TO DATE)

3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

E MELOXICAM/CN 5
L53 1 S E3

L53 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 71125-38-7 REGISTRY
CN 2H-1,2-Benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-, 1,1-dioxide (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Meloxicam**
CN Metacam
CN Mobec
CN Mobic
CN Mobicox
CN Movalis
CN UH-AC 62XX
FS 3D CONCORD
DR 133687-22-6
MF C14 H13 N3 O4 S2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PHARMASEARCH, PROMT, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: WHO



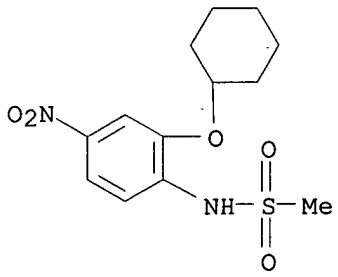
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

443 REFERENCES IN FILE CA (1957 TO DATE)
13 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
444 REFERENCES IN FILE CAPLUS (1957 TO DATE)

E NS398/CN 5
E "NS-398"/CN 5
E "NS 398"/CN 5
L54 1 S E3

L54 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 123653-11-2 REGISTRY

CN Methanesulfonamide, N-[2-(cyclohexyloxy)-4-nitrophenyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN N-(2-Cyclohexyloxy-4-nitrophenyl)methanesulfonamide
CN **NS 398**
CN Taisho NS 398
FS 3D CONCORD
MF C13 H18 N2 O5 S
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CIN, CSCHEM, DRUGNL, DRUGUPDATES, EMBASE, MEDLINE, PHAR, PROMT, SYNTHLINE, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

335 REFERENCES IN FILE CA (1957 TO DATE)
5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
336 REFERENCES IN FILE CAPLUS (1957 TO DATE)

		E CYCLOOXYGENASE 2/CN 5
L1	2	S E3-E4
		E "CYCLOOXYGENASE-2"/CN 5
L2	8	S "CYCLOOXYGENASE-2"?/CN
		E "TAISHO NS-398"/CN 5
L3	1	S E2
		E FLOSULIDE/CN 5
L4	1	S E3
		E "MERCK MK-966"/CN 5
		E MK 966/CN 5
L5	1	S E3
		E L 752/CN
L6	1	S E5
L7	14	S L1 OR L2 OR L3 OR L4 OR L5 OR L6
		E LEUKOTRIENE B4/CN 5
L8	1	S E3
		E "BAY-X-1005"/CN 5
		E CGS 25019C/CN 5
L9	1	S E3
		E "BAY X1005"/CN 5
		E "BAY X 1005"/CN 5

Searcher : Shears 308-4994

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                E EBSELEN/CN 5
L10           1 S E3
                E ETH 615/CN 5
L11           1 S E3
                E LY 293111/CN 5
L12           1 S E3
                E ONO 4057/CN 5
L13           1 S E3
                E TMK 688/CN 5
L14           1 S E3
                E BI RM270/CN 5
                E B1 RM270/CN 5
                E B1RM270/CN 5
                E BOEHRINGER INGLEHEIM/CN
                E B1 RM 270/CN 5
                E BI RM 270/CN 5
                E LY 213024/CN 5
L15           1 S E3
                E LY 264086/CN 5
L16           1 S E3
                E LY 292728/CN 5
L17           1 S E3
                E ONO LB457/CN 5
                E ONO LB 457/CN 5
                E PFIZER 105696/CN 5
L18           1 S E3
                E PF 10042/CN 5
L19           1 S E3
                E RP 66153/CN 5
L20           1 S E3
                E SB 201146/CN 5
L21           1 S E3
                E SB 201993/CN 5
L22           1 S E3
                E SC 53228/CN 5
L23           1 S E3
                E SM 15178/CN 5
L24           1 S E3
                E WAY 121006/CN 5
L25           1 S E3
                E BAY O 8276/CN 5
                E O 8276/CN 5
                E BAY 0 8276/CN 5
L26           1 S E4
                E CALCITRIOL/CN 5
L27           1 S E3
                E CI 987/CN 5
L28           1 S E3
                E L 651392/CN 5
L29           1 S E3
                E LY 210073/CN 5
L30           1 S E3
                E LY 223982/CN 5
L31           1 S E3
                E LY 233569/CN 5
L32           1 S E3
                E LY 255283/CN 5
L33           1 S E3
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                E MK 591/CN 5
L34           1 S E3
                E MK 886/CN 5
L35           1 S E3
                E ONO LB 448/CN 5
                E "ONO LB-448"/CN 5
                E ONO LB448/CN 5
                E PF 5901/CN 5
L36           1 S E3
                E RG 14893/CN 5
L37           1 S E3
                E RG 66364/CN 5
                E RG 69698/CN 5
                E SC 41930/CN 5
L38           1 S E3
                E SC 50505/CN 5
L39           1 S E3
                E SC 51146/CN 5
L40           1 S E3
                E SKF 104493/CN 5
L41           1 S E3
                E TEI 1338/CN 5
L42           1 S E3
                SAV TEMP L7 EPP1/A
L43          35 S L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L
                SAV TEMP L43 EPP2/A

                E FLOCULIDE/CN 5
L52           1 S E3
                E MELOXICAM/CN 5
L53           1 S E3
                E NS398/CN 5
                E "NS-398"/CN 5
                E "NS 398"/CN 5
L54           1 S E3
L55           3 S L52 OR L53 OR L54


                E RP 66364/CN 5
L59           1 S E3
                E RP 69698/CN 5
L60           1 S E3
                E "ONO-LB 448"/CN 5
L61           1 S E3
L62          38 S L43 OR L59 OR L60 OR L61


                E "BI-RM-270"/CN 5
L65           1 S 147432-77-7/RN

     FILE 'HCAPLUS' ENTERED AT 15:58:22 ON 11 JUN 2003
L1            2 SEA FILE=REGISTRY ABB=ON  PLU=ON  ("CYCLOOXYGENASE 2"/CN
                OR "CYCLOOXYGENASE 2 (HUMAN CLONE 23B/9C GENE HCOX-2)"/CN
                )
L2            8 SEA FILE=REGISTRY ABB=ON  PLU=ON  "CYCLOOXYGENASE-2"?/CN

L3            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "TAISHO NS 398"/CN
L4            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  FLOSULIDE/CN
```

L5	1	SEA FILE=REGISTRY ABB=ON PLU=ON "MK 966"/CN
L6	1	SEA FILE=REGISTRY ABB=ON PLU=ON "L 752860"/CN
L7	14	SEA FILE=REGISTRY ABB=ON PLU=ON L1 OR L2 OR L3 OR L4 OR L5 OR L6
L8	1	SEA FILE=REGISTRY ABB=ON PLU=ON "LEUKOTRIENE B4"/CN
L9	1	SEA FILE=REGISTRY ABB=ON PLU=ON "CGS 25019C"/CN
L10	1	SEA FILE=REGISTRY ABB=ON PLU=ON EBSELEN/CN
L11	1	SEA FILE=REGISTRY ABB=ON PLU=ON "ETH 615"/CN
L12	1	SEA FILE=REGISTRY ABB=ON PLU=ON "LY 293111"/CN
L13	1	SEA FILE=REGISTRY ABB=ON PLU=ON "ONO 4057"/CN
L14	1	SEA FILE=REGISTRY ABB=ON PLU=ON "TMK 688"/CN
L15	1	SEA FILE=REGISTRY ABB=ON PLU=ON "LY 213024"/CN
L16	1	SEA FILE=REGISTRY ABB=ON PLU=ON "LY 264086"/CN
L17	1	SEA FILE=REGISTRY ABB=ON PLU=ON "LY 292728"/CN
L18	1	SEA FILE=REGISTRY ABB=ON PLU=ON "PFIZER 105696"/CN
L19	1	SEA FILE=REGISTRY ABB=ON PLU=ON "PF 10042"/CN
L20	1	SEA FILE=REGISTRY ABB=ON PLU=ON "RP 66153"/CN
L21	1	SEA FILE=REGISTRY ABB=ON PLU=ON "SB 201146"/CN
L22	1	SEA FILE=REGISTRY ABB=ON PLU=ON "SB 201993"/CN
L23	1	SEA FILE=REGISTRY ABB=ON PLU=ON "SC 53228"/CN
L24	1	SEA FILE=REGISTRY ABB=ON PLU=ON "SM 15178"/CN
L25	1	SEA FILE=REGISTRY ABB=ON PLU=ON "WAY 121006"/CN
L26	1	SEA FILE=REGISTRY ABB=ON PLU=ON "BAY 0-8276"/CN
L27	1	SEA FILE=REGISTRY ABB=ON PLU=ON CALCITRIOL/CN
L28	1	SEA FILE=REGISTRY ABB=ON PLU=ON "CI 987"/CN
L29	1	SEA FILE=REGISTRY ABB=ON PLU=ON "L 651392"/CN
L30	1	SEA FILE=REGISTRY ABB=ON PLU=ON "LY 210073"/CN
L31	1	SEA FILE=REGISTRY ABB=ON PLU=ON "LY 223982"/CN
L32	1	SEA FILE=REGISTRY ABB=ON PLU=ON "LY 233569"/CN
L33	1	SEA FILE=REGISTRY ABB=ON PLU=ON "LY 255283"/CN
L34	1	SEA FILE=REGISTRY ABB=ON PLU=ON "MK 591"/CN
L35	1	SEA FILE=REGISTRY ABB=ON PLU=ON "MK 886"/CN
L36	1	SEA FILE=REGISTRY ABB=ON PLU=ON "PF 5901"/CN
L37	1	SEA FILE=REGISTRY ABB=ON PLU=ON "RG 14893"/CN
L38	1	SEA FILE=REGISTRY ABB=ON PLU=ON "SC 41930"/CN
L39	1	SEA FILE=REGISTRY ABB=ON PLU=ON "SC 50505"/CN
L40	1	SEA FILE=REGISTRY ABB=ON PLU=ON "SC 51146"/CN
L41	1	SEA FILE=REGISTRY ABB=ON PLU=ON "SKF 104493"/CN
L42	1	SEA FILE=REGISTRY ABB=ON PLU=ON "TEI 1338"/CN
L43	35	SEA FILE=REGISTRY ABB=ON PLU=ON L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 OR L32 OR L33 OR L34 OR L35 OR L36 OR L37 OR L38 OR L39 OR L40 OR L41 OR L42
L44	8311	SEA FILE=HCAPLUS ABB=ON PLU=ON (COX OR CYCLOOXYGENASE OR CYCLO OXYGENASE)(2A)(2 OR II) OR COX2 OR COXII OR L7 OR TAISHO(W)(NS398 OR NS 398) OR FLOSULIDE OR MK966 OR MK 966 OR ("L752" OR L 752)(W)860 OR L752860 OR L 752860
L45	15005	SEA FILE=HCAPLUS ABB=ON PLU=ON L43 OR LEUKOTREINE B4 OR X1005 OR X 1005 OR CGS 25019C OR CGS25019C OR ETH615 OR ETH 615 OR EBSELEN OR LY293111 OR LY(W)(293111 OR 213024 OR 264086 OR 292728) OR LY213024 OR LY264086 OR LY292728 OR ONO(W)(4057 OR LB457 OR LB 457) OR ONO4057 OR TMK688 OR TMK 688
L46	102	SEA FILE=HCAPLUS ABB=ON PLU=ON BIRM270 OR BI(W)(RM270 OR RM 270) OR PFIZER 105696 OR PF10042 OR PF(W)(10042 OR 5901) OR RP66153 OR RP 66153 OR SB(W)(201146 OR 201993) OR SB201146 OR SB201993 OR SC53228 OR SC41930 OR SC50505

Searcher : Shears 308-4994

		OR SC51146 OR SC(W)(53228 OR 41930 OR 50505 OR 51146) OR SF5901
L47	384	SEA FILE=HCAPLUS ABB=ON PLU=ON SKF104493 OR SK(W)F(W)104493OR TEI1338 OR TEI 1338 OR RG14893 OR RG66364 OR RG69698 OR RG(W)(14893 OR 66364 OR 69698) OR ONOLB448 OR ONO(W)(LB448 OR LB 448) OR MK591 OR MK886 OR MK(W)(591 OR 886) OR LY210073 OR LY223982 OR LY233569 OR LY255283
L48	2827	SEA FILE=HCAPLUS ABB=ON PLU=ON LY(W)(210073 OR 223982 OR 233569 OR 255283) OR CI987 OR CI 987 OR L651392 OR L 651392 OR CALCITRIOL OR O8276 OR O 8276 OR SM15178 OR SM 15178 OR WAY121006 OR WAY 121006
L52	1	SEA FILE=REGISTRY ABB=ON PLU=ON FLOCULIDE/CN
L53	1	SEA FILE=REGISTRY ABB=ON PLU=ON MELOXICAM/CN
L54	1	SEA FILE=REGISTRY ABB=ON PLU=ON "NS 398"/CN
L55	3	SEA FILE=REGISTRY ABB=ON PLU=ON L52 OR L53 OR L54
L59	1	SEA FILE=REGISTRY ABB=ON PLU=ON "RP 66364"/CN
L60	1	SEA FILE=REGISTRY ABB=ON PLU=ON "RP 69698"/CN
L61	1	SEA FILE=REGISTRY ABB=ON PLU=ON "ONO-LB 448"/CN
L65	1	SEA FILE=REGISTRY ABB=ON PLU=ON 147432-77-7/RN
L69	76	SEA FILE=HCAPLUS ABB=ON PLU=ON (L44 OR L55 OR FLO!ULIDE OR MELOXICAM OR NS398 OR NS 398)(L)(L45 OR L46 OR L47 OR L48 OR L59 OR L60 OR L61 OR L65 OR LEUKOTRIENE B4 OR BAY(W)(08276 OR 0 8276) OR SKF 104493 OR RP66364 OR RP69698 OR RP(W)(66364 OR 69698) OR MK(W)(591 OR 886) OR TEI 1338 OR RG 14893 OR ONO LB 448)
L70	33	SEA FILE=HCAPLUS ABB=ON PLU=ON L69(L)(TREAT? OR THERAP?)
L75	22	SEA FILE=HCAPLUS ABB=ON PLU=ON L70(L)INFLAMM?
L1	2	SEA FILE=REGISTRY ABB=ON PLU=ON ("CYCLOOXYGENASE 2"/CN OR "CYCLOOXYGENASE 2 (HUMAN CLONE 23B/9C GENE HCOX-2)"/CN)
L2	8	SEA FILE=REGISTRY ABB=ON PLU=ON "CYCLOOXYGENASE-2"?/CN
L3	1	SEA FILE=REGISTRY ABB=ON PLU=ON "TAISHO NS 398"/CN
L4	1	SEA FILE=REGISTRY ABB=ON PLU=ON FLOSULIDE/CN
L5	1	SEA FILE=REGISTRY ABB=ON PLU=ON "MK 966"/CN
L6	1	SEA FILE=REGISTRY ABB=ON PLU=ON "L 752860"/CN
L7	14	SEA FILE=REGISTRY ABB=ON PLU=ON L1 OR L2 OR L3 OR L4 OR L5 OR L6
L8	1	SEA FILE=REGISTRY ABB=ON PLU=ON "LEUKOTRIENE B4"/CN
L9	1	SEA FILE=REGISTRY ABB=ON PLU=ON "CGS 25019C"/CN
L10	1	SEA FILE=REGISTRY ABB=ON PLU=ON EBSELEN/CN
L11	1	SEA FILE=REGISTRY ABB=ON PLU=ON "ETH 615"/CN
L12	1	SEA FILE=REGISTRY ABB=ON PLU=ON "LY 293111"/CN
L13	1	SEA FILE=REGISTRY ABB=ON PLU=ON "ONO 4057"/CN
L14	1	SEA FILE=REGISTRY ABB=ON PLU=ON "TMK 688"/CN
L15	1	SEA FILE=REGISTRY ABB=ON PLU=ON "LY 213024"/CN
L16	1	SEA FILE=REGISTRY ABB=ON PLU=ON "LY 264086"/CN
L17	1	SEA FILE=REGISTRY ABB=ON PLU=ON "LY 292728"/CN
L18	1	SEA FILE=REGISTRY ABB=ON PLU=ON "PFIZER 105696"/CN
L19	1	SEA FILE=REGISTRY ABB=ON PLU=ON "PF 10042"/CN
L20	1	SEA FILE=REGISTRY ABB=ON PLU=ON "RP 66153"/CN
L21	1	SEA FILE=REGISTRY ABB=ON PLU=ON "SB 201146"/CN
L22	1	SEA FILE=REGISTRY ABB=ON PLU=ON "SB 201993"/CN
L23	1	SEA FILE=REGISTRY ABB=ON PLU=ON "SC 53228"/CN

L24	1	SEA FILE=REGISTRY ABB=ON PLU=ON "SM 15178"/CN
L25	1	SEA FILE=REGISTRY ABB=ON PLU=ON "WAY 121006"/CN
L26	1	SEA FILE=REGISTRY ABB=ON PLU=ON "BAY 0-8276"/CN
L27	1	SEA FILE=REGISTRY ABB=ON PLU=ON CALCITRIOL/CN
L28	1	SEA FILE=REGISTRY ABB=ON PLU=ON "CI 987"/CN
L29	1	SEA FILE=REGISTRY ABB=ON PLU=ON "L 651392"/CN
L30	1	SEA FILE=REGISTRY ABB=ON PLU=ON "LY 210073"/CN
L31	1	SEA FILE=REGISTRY ABB=ON PLU=ON "LY 223982"/CN
L32	1	SEA FILE=REGISTRY ABB=ON PLU=ON "LY 233569"/CN
L33	1	SEA FILE=REGISTRY ABB=ON PLU=ON "LY 255283"/CN
L34	1	SEA FILE=REGISTRY ABB=ON PLU=ON "MK 591"/CN
L35	1	SEA FILE=REGISTRY ABB=ON PLU=ON "MK 886"/CN
L36	1	SEA FILE=REGISTRY ABB=ON PLU=ON "PF 5901"/CN
L37	1	SEA FILE=REGISTRY ABB=ON PLU=ON "RG 14893"/CN
L38	1	SEA FILE=REGISTRY ABB=ON PLU=ON "SC 41930"/CN
L39	1	SEA FILE=REGISTRY ABB=ON PLU=ON "SC 50505"/CN
L40	1	SEA FILE=REGISTRY ABB=ON PLU=ON "SC 51146"/CN
L41	1	SEA FILE=REGISTRY ABB=ON PLU=ON "SKF 104493"/CN
L42	1	SEA FILE=REGISTRY ABB=ON PLU=ON "TEI 1338"/CN
L43	35	SEA FILE=REGISTRY ABB=ON PLU=ON L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 OR L32 OR L33 OR L34 OR L35 OR L36 OR L37 OR L38 OR L39 OR L40 OR L41 OR L42
L44	8311	SEA FILE=HCAPLUS ABB=ON PLU=ON (COX OR CYCLOOXYGENASE OR CYCLO OXYGENASE)(2A)(2 OR II) OR COX2 OR COXII OR L7 OR TAISHO(W)(NS398 OR NS 398) OR FLOSULIDE OR MK966 OR MK 966 OR ("L752" OR L 752)(W)860 OR L752860 OR L 752860
L45	15005	SEA FILE=HCAPLUS ABB=ON PLU=ON L43 OR LEUKOTREINE B4 OR X1005 OR X 1005 OR CGS 25019C OR CGS25019C OR ETH615 OR ETH 615 OR EBSELEN OR LY293111 OR LY(W)(293111 OR 213024 OR 264086 OR 292728) OR LY213024 OR LY264086 OR LY292728 OR ONO(W)(4057 OR LB457 OR LB 457) OR ONO4057 OR TMK688 OR TMK 688
L46	102	SEA FILE=HCAPLUS ABB=ON PLU=ON BIRM270 OR BI(W)(RM270 OR RM 270) OR PFIZER 105696 OR PF10042 OR PF(W)(10042 OR 5901) OR RP66153 OR RP 66153 OR SB(W)(201146 OR 201993) OR SB201146 OR SB201993 OR SC53228 OR SC41930 OR SC50505 OR SC51146 OR SC(W)(53228 OR 41930 OR 50505 OR 51146) OR SF5901
L47	384	SEA FILE=HCAPLUS ABB=ON PLU=ON SKF104493 OR SK(W)F(W)104493OR TEI1338 OR TEI 1338 OR RG14893 OR RG66364 OR RG69698 OR RG(W)(14893 OR 66364 OR 69698) OR ONOLB448 OR ONO(W)(LB448 OR LB 448) OR MK591 OR MK886 OR MK(W)(591 OR 886) OR LY210073 OR LY223982 OR LY233569 OR LY255283
L48	2827	SEA FILE=HCAPLUS ABB=ON PLU=ON LY(W)(210073 OR 223982 OR 233569 OR 255283) OR CI987 OR CI 987 OR L651392 OR L 651392 OR CALCITRIOL OR O8276 OR O 8276 OR SM15178 OR SM 15178 OR WAY121006 OR WAY 121006
L52	1	SEA FILE=REGISTRY ABB=ON PLU=ON FLOCULIDE/CN
L53	1	SEA FILE=REGISTRY ABB=ON PLU=ON MELOXICAM/CN
L54	1	SEA FILE=REGISTRY ABB=ON PLU=ON "NS 398"/CN
L55	3	SEA FILE=REGISTRY ABB=ON PLU=ON L52 OR L53 OR L54
L59	1	SEA FILE=REGISTRY ABB=ON PLU=ON "RP 66364"/CN
L60	1	SEA FILE=REGISTRY ABB=ON PLU=ON "RP 69698"/CN
L61	1	SEA FILE=REGISTRY ABB=ON PLU=ON "ONO-LB 448"/CN
L65	1	SEA FILE=REGISTRY ABB=ON PLU=ON 147432-77-7/RN
L69	76	SEA FILE=HCAPLUS ABB=ON PLU=ON (L44 OR L55 OR FLO!ULIDE

OR MELOXICAM OR NS398 OR NS 398)(L)(L45 OR L46 OR L47 OR L48 OR L59 OR L60 OR L61 OR L65 OR LEUKOTRIENE B4 OR BAY(W)(08276 OR 0 8276) OR SKF 104493 OR RP66364 OR RP69698 OR RP(W)(66364 OR 69698) OR MK(W)(591 OR 886) OR TEI 1338 OR RG 14893 OR ONO LB 448)

L77 26 SEA FILE=HCAPLUS ABB=ON PLU=ON L69(L)(ANTIINFLAMM? OR ANTI INFLAMM?)

=> s l75 or l77

L79 39 L75 OR L77

L79 ANSWER 1 OF 39 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:343942 HCAPLUS

TITLE: LAAE-14, a new in vitro inhibitor of intracellular calcium mobilization, modulates acute and chronic inflammation

AUTHOR(S): Lucas, Rut; Alves, Mario; del Olmo, Esther; San Feliciano, Arturo; Paya, Miguel

CORPORATE SOURCE: Av. V. Andres Estelles s/n, Departamento de Farmacologia, Universidad de Valencia, Valencia, Burjassot, 46100, Spain

SOURCE: Biochemical Pharmacology (2003), 65(9), 1539-1549
CODEN: BCPCA6; ISSN: 0006-2952

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A new lipidic acid-amido ether deriv. (LAAE-14) able to reduce dose-dependently the calcium increases mediated either by calcium ionophore ionomycin, by the endoplasmic reticular Ca2+-ATPase inhibitor thapsigargin, or by the chemotactic tripeptide N-formyl-l-methionyl-l-leucyl-l-phenylalanine (fMLP), in human neutrophils as well as in murine peritoneal macrophages, but not ATP, has been evaluated as a potential **anti-inflammatory** drug. This compd. attenuated leukocyte activation by means of its inhibitory effect on the respiratory burst elicited in both types of cells by 12-O-tetradecanoyl phorbol 13-acetate, by inhibition of the degranulation process induced by cytochalasin B+fMLP or cytochalasin B+platelet activating factor, as well as by redn. of **leukotriene B4** synthesis induced by the calcium ionophore A23187. In addn., in zymosan-stimulated mouse peritoneal macrophages LAAE-14 caused a potent inhibition of nitrite and prostaglandin E2 prodn. This compd. exerted acute and chronic **anti-inflammatory** effects by oral route, that may be related with several mechanisms such as attenuation of leukocyte activation, inhibition of inducible nitric oxide synthase, **cyclo-oxygenase-2** and cytosolic phospholipase A2 expression as well as redn. in tumor necrosis factor-.alpha. prodn. Its **anti-inflammatory** profile is clearly correlated with its behavior as inhibitor of intracellular calcium mobilization. The profile and potency of this compd. may have relevance for the inhibition of the inflammatory response at different levels and may represent a new approach to the development of new **anti-inflammatory** drugs.

L79 ANSWER 2 OF 39 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:804185 HCAPLUS
TITLE: Cyclooxygenase and 5-lipoxygenase inhibitors protect against mononuclear phagocyte neurotoxicity
AUTHOR(S): Klegeris, Andis; McGeer, Patrick L.
CORPORATE SOURCE: Kinsmen Laboratory of Neurological Research, University of British Columbia, Vancouver, BC, V6T 1Z3, Can.
SOURCE: Neurobiology of Aging (2002), 23(5), 787-794
CODEN: NEAGDO; ISSN: 0197-4580
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Neuroinflammation and oxidative stress are believed to be contributing factors to neurodegeneration in normal aging, as well as in age-related neurol. disorders. Reactive microglia are found in increased nos. in aging brain and are prominently assocd. with lesions in such age-related degenerative conditions as Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). In vitro, stimulated microglia or microglial-like cells secrete neurotoxic materials and are generators of free radicals through their respiratory burst system. Agents that suppress microglial activation are therefore candidates for neuroprotection. We have developed quant. in vitro assays for measuring neurotoxicity of microglia or other mononuclear phagocytes. Neuronal like SH-SY5Y cells are cultured in supernatants from activated cells of the human monocytic THP-1 line and their survival is followed. Respiratory burst is directly measured on the activated cells. We tested inhibitors of the cyclooxygenase (COX) or the 5-lipoxygenase (5-LOX) pathways as possible neuroprotective agents. The COX pathway generates **inflammatory** prostaglandins, while the 5-LOX pathway generates **inflammatory** leukotrienes. We found that inhibitors of both these pathways suppressed neurotoxicity in a dose-dependent fashion. They included the COX-1 inhibitor indomethacin; the **COX-2** inhibitor **NS-398**; the mixed **COX-1/COX-2** inhibitor ibuprofen; the nitric oxide (NO) derivs. of indomethacin, ibuprofen and flurbiprofen; the 5-LOX inhibitor REV 5901; and the 5-LOX activating protein (FLAP) inhibitor **MK-886**. The FLAP inhibitor also reduced respiratory burst activity in a more potent manner than indomethacin. Combinations of COX and 5-LOX inhibitors were more effective than single inhibitors. The data suggest that both COX inhibitors and 5-LOX inhibitors may be neuroprotective in vivo by suppressing toxic actions of microglia/macrophages, and that combinations of the two might have greater **therapeutic** potential than single inhibitors of either class.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 3 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:781072 HCAPLUS
DOCUMENT NUMBER: 138:331134
TITLE: Pharmacodynamics and pharmacokinetics of phenylbutazone in calves
AUTHOR(S): Arifah, A. K.; Lees, P.

CORPORATE SOURCE: The Royal Veterinary College, Hatfield, Hertfordshire, UK
SOURCE: Journal of Veterinary Pharmacology and Therapeutics (2002), 25(4), 299-309
CODEN: JVPTD9; ISSN: 0140-7783
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Phenylbutazone (PBZ) was administered to six calves i.v. and orally at a dose rate of 4.4 mg/kg in a three-period cross-over study incorporating a placebo **treatment** to establish its pharmacokinetic and pharmacodynamic properties. Extravascular distribution was detd. by measuring penetration into tissue chamber fluid in the absence of stimulation (transudate) and after stimulation of chamber tissue with the mild irritant carrageenan (exudate). PBZ pharmacokinetics after i.v. dosage was characterized by slow clearance (1.29 mL/kg/h), long-terminal half-life (53.4 h), low distribution vol. (0.09 L/kg) and low concns. in plasma of the metabolite oxyphenbutazone (OPBZ), confirming previously published data for adult cattle. After oral dosage bioavailability (F) was 66%. Passage into exudate was slow and limited, and penetration into transudate was even slower and more limited; area under curve values for plasma, exudate and transudate after i.v. dosage were 3604, 1117 and 766 .mu.g h/mL and corresponding values after oral dosage were 2435, 647 and 486 .mu.g h/mL. These concns. were approx. 15-20 (plasma) and nine (exudate) times greater than those previously reported in horses (receiving the same dose rate of PBZ). In the horse, the lower concns. had produced marked inhibition of eicosanoid synthesis and suppressed the **inflammatory** response. The higher concns. in calves were insufficient to inhibit significantly exudate prostaglandin E2 (PGE2), **leukotriene B4** (LTB4) and .beta.-glucuronidase concns. and exudate leukocyte nos., serum thromboxane B2 (TxB2), and bradykinin-induced skin swelling. These differences from the horse might be the result of: (a) the presence in equine biol. fluids of higher concns. than in calves of the active PBZ metabolite, OPBZ; (b) a greater degree of binding of PBZ to plasma protein in calves; (c) species differences in the sensitivity to PBZ of the cyclo-oxygenase (COX) isoenzymes, COX-1 and **COX-2** or; (d) a combination of these factors. To achieve clin. efficacy with single doses of PBZ in calves, higher dosages than 4.4 mg/kg will be probably required.

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 4 OF 39 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:594628 HCAPLUS
DOCUMENT NUMBER: 137:150265

TITLE: Substituted aryl compounds as novel cyclooxygenase-2 selective inhibitors, compositions and methods of use

INVENTOR(S): Khanapure, Subhash P.; Garvey, David S.; Earl, Richard A.; Ezawa, Maiko; Fang, Xinqin; Gaston, Ricky D.
PATENT ASSIGNEE(S): Nitromed, Inc., USA

SOURCE: PCT Int. Appl., 132 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002060378	A2	20020808	WO 2001-US48823	20011221

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002119977	A1	20020829	US 2001-24046	20011221

PRIORITY APPLN. INFO.: US 2000-256932P P 20001221
OTHER SOURCE(S): MARPAT 137:150265

AB Substituted aryl compds. that are **cyclooxygenase 2** (**COX-2**) selective inhibitors and compns. comprising at least one **COX-2** selective inhibitor, and, optionally, at least one compd. that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, and/or, optionally, at least one **therapeutic** agent are described. A **therapeutic** agent is selected from steroids, nonsteroidal **anti-inflammatory** compds. (NSAID), 5-lipoxygenase (5-LO) inhibitors, **leukotriene B4** (LTB4) receptor antagonists, leukotriene A4 (LTA4) hydrolase inhibitors, 5-HT agonists, 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) inhibitors, H2 antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating antihistaminics, inducible nitric oxide synthase inhibitors, opioids, analgesics, Helicobacter pylori inhibitors, proton pump inhibitors, and isoprostane inhibitors. The invention also provides novel kits comprising at least one **COX-2** selective inhibitor, and, optionally, at least one nitric oxide donor, and/or, optionally, at least one **therapeutic** agent. The **cyclooxygenase -2** selective inhibitors of the invention can be optionally nitrosated and/or nitrosylated. The invention also provides methods for **treating inflammation**, pain and fever; for **treating** and/or improving the gastrointestinal properties of **COX-2** selective inhibitors; for facilitating wound healing; for **treating** and/or preventing renal toxicity or other toxicities; for **treating** and/or preventing other disorders resulting from elevated levels of **cyclooxygenase -2**; and for improving the cardiovascular profile of **COX-2** selective inhibitors.

L79 ANSWER 5 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:295966 HCAPLUS
DOCUMENT NUMBER: 137:195230

TITLE: The mechanism of action of the new anti-inflammatory compound ML3000: inhibition of 5-LOX and COX-1/2
AUTHOR(S): Tries, S.; Neupert, W.; Laufer, S.
CORPORATE SOURCE: Preclinical Development, Merckle GmbH, Blaubeuren, DE-89135, Germany
SOURCE: Inflammation Research (2002), 51(3), 135-143
CODEN: INREFB; ISSN: 1023-3830
PUBLISHER: Birkhaeuser Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This work examd. the effects of ML3000 and other nonsteroidal **anti-inflammatory** drugs (NSAIDs) (indomethacin, diclofenac) on the synthesis of 5-lipoxygenase (5-LOX) products (LTB4, LTC4) and cyclooxygenase (**COX**)-1 and -**2** products (TXB2, PGE2) in vitro and ex vivo in order to further elucidate the mechanism of action of ML3000. The effect of ML3000 on the shunt of arachidonic acid to the LOX pathway when COX is blocked was studied in a human whole-blood assay. ML3000 (0.3, 1, 3, 10, 30 .mu.g/mL) and indomethacin (0.3, 1, 3, 10, 30 .mu.g/mL) concn.-dependently inhibited the synthesis of PGE2 (IC50 = 3.9 and 4.5 .mu.M, resp.). In contrast to ML3000, indomethacin increased LTC4 by .ltoreq.155.5% of control values. 5-LOX inhibition was further tested in a basophilic leukemia cell assay using RBL-1 cells. ML3000 (1-10 .mu.M) inhibited the synthesis of LTB4 in a concn.-related manner (IC50: 3.6 .mu.M). In carrageenan- induced rat paw edema, ML3000 and indomethacin completely blocked the formation of PGE2 in the inflamed tissue. LTB4 prodn. in the inflamed paw was reduced to basal levels by ML3000, whereas LTB4 concns. remained markedly elevated after indomethacin. 5-LOX inhibition in the inflamed rat colon was investigated by measuring LTB4 synthesis. **MK-886** and ML3000 at 10 mg/kg orally reduced LTB4 prodn. as compared to that in controls. LTB4 levels in the rat stomach were comparable to control values after oral administration of ML3000 (10, 30, 100 mg/kg), whereas oral **treatment** with indomethacin (0.3, 1, 3 mg/kg) or diclofenac (1, 3 mg/kg) increased LTB4. These results provide further evidence, that ML3000 inhibits 5-LOX as well as COX-1 and **COX-2** in vitro and in animal expts. The favorable gastrointestinal tolerability of the compd. is believed to be linked to the mechanism of combined 5-LOX and **COX**-1/**2** inhibition by ML3000.

REFERENCE COUNT: 78 THERE ARE 78 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 6 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:241647 HCAPLUS
DOCUMENT NUMBER: 137:153683
TITLE: Synthesis of interleukin 1.beta., tumor necrosis factor-.alpha., and interstitial collagenase (MMP-1) is eicosanoid dependent in human osteoarthritis synovial membrane explants: Interactions with antiinflammatory cytokines
AUTHOR(S): He, Wendy; Pelletier, Jean-Pierre; Martel-Pelletier, Johanne; Laufer, Stefan; Di Battista, John A.
CORPORATE SOURCE: Osteoarthritis Research Unit, Hospital

Notre-Dame, Centre Hospitalier de l'Universite de Montreal, Montreal, QC, H2L 4M1, Can.
SOURCE: Journal of Rheumatology (2002), 29(3), 546-553
CODEN: JRHUA9; ISSN: 0315-162X
PUBLISHER: Journal of Rheumatology Publishing Co. Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To det. the level of **leukotriene B4** (LTB4) synthesized and released by synovium of patients with osteoarthritis (OA), and to study the role of lipoxygenase (LO)/cyclooxygenase (COX) products on proinflammatory cytokine and interstitial collagenase (MMP-1) synthesis. Human OA synovial explants were cultured in the presence of lipopolysaccharide (L) and the ionophores ionomycin (I) and thapsigargin (T) (LIT) for 72 h at 37.degree.C, and LTB4 released into the culture medium was measured in the absence or presence of a **COX-2**-specific inhibitor, **NS-398**, or the 5-LO activating protein inhibitor Bay-**x-1005**. Increasing concns. of LTB4 (10-9 to 10-6 M) were incubated with explants for 24 h at 37.degree.C, and interleukin 1.beta. (IL-1.beta.) and tumor necrosis factor-.alpha. (TNF-.alpha.) in the conditioned medium were quantitated by ELISA. The effect of endogenous eicosanoids on basal and induced levels of IL-1.beta., TNF-.alpha., and MMP-1 synthesis was examd. by incubating explants in the presence of **NS-398** and Bay-**x-1005**. The effect of **antiinflammatory** cytokines rhIL-4, IL-10, and IL-13 on basal and LTB4 dependent stimulation of IL-1.beta./TNF-.alpha. synthesis was studied under titrn. conditions. Physiol. relevant concns. (10-10 to 10-9 mol/l) of LTB4 were produced in the presence of LIT. Bay-**x-1005** abrogated LTB4 release, while **NS-398** was without effect. LTB4 stimulated IL-1.beta. and TNF-.alpha. synthesis with an EC50 of 190 .+-. 35 and 45 .+-. 9 nmol/l, resp. Significant concns. of IL-1.beta. and TNF-.alpha. were released (100-200 and 500-600 pg/mL, resp.). Basal and LIT induced IL-1.beta. and TNF-.alpha. prodn. were inhibited by Bay-**x-1005** in a dose dependent manner, while the addn. of **NS-398** caused a potent stimulatory effect. The preferential **COX-2** inhibitor also induced MMP-1 synthesis in a manner essentially identical to the proinflammatory cytokines. The **antiinflammatory** cytokine IL-4 blocked LTB4 dependent stimulation of IL-1.beta. and TNF-.alpha. synthesis. In contrast, IL-10 markedly stimulated both cytokines when incubated alone or in the presence of LTB4 where the effect was additive. Endogenous and locally produced eicosanoids regulate proinflammatory cytokine and MMP-1 synthesis under basal and stimulated conditions in vitro, with leukotrienes and prostaglandins having opposite effects in general. The clin. use of **antiinflammatory** drugs that inhibit eicosanoid synthesis requires an appreciation of their relative capacity to inhibit LO/COX in order to predict their effect on the synthesis of proinflammatory cytokines and matrix metalloproteases. IL-10 stimulated proinflammatory cytokine synthesis in our ex vivo culture system.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 7 OF 39 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:100331 HCAPLUS
DOCUMENT NUMBER: 136:379625
TITLE: Ebselen, a glutathione peroxidase mimetic seleno-organic compound, as a multifunctional antioxidant: implication for inflammation-associated carcinogenesis
AUTHOR(S): Nakamura, Yoshimasa; Feng, Qing; Kumagai, Takeshi; Torikai, Koji; Ohigashi, Hajime; Osawa, Toshihiko; Noguchi, Noriko; Niki, Etsuo; Uchida, Koji
CORPORATE SOURCE: Laboratory of Food and Biodynamics, Graduate School of Bioagricultural Sciences, Nagoya University, Nagoya, 464-8601, Japan
SOURCE: Journal of Biological Chemistry (2002), 277(4), 2687-2694
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Ebselen**, a seleno-org. compd. showing glutathione peroxidase-like activity, is one of the promising synthetic antioxidants. In the present study, we investigated the antioxidant activities of **ebselen** using a 12-O-tetradecanoylphorbol-13-acetate (TPA)-**treated** mouse skin model. Double pretreatments of mouse skin with **ebselen** significantly inhibited TPA-induced formation of thiobarbituric acid-reacting substance, known as an overall oxidative damage biomarker, in mouse epidermis, suggesting that **ebselen** indeed acts as an antioxidant in mouse skin. The antioxidative effect of **ebselen** is attributed to its selective blockade of leukocyte infiltration and activation leading to attenuation of the H2O2 level. In in vitro studies, **ebselen** inhibited TPA-induced superoxide generation in differentiated HL-60 cells and lipopolysaccharide-induced **cyclooxygenase-2** protein expression in RAW 264.7 cells. In addn., we demonstrated for the first time that **ebselen** potentiated phase II enzyme activities, including NAD(P)H:(quinone-acceptor) oxidoreductase 1 and glutathione S-transferase in cultured hepatocytes and in mouse skin. These results strongly suggest that **ebselen**, a multifunctional antioxidant, is a potential chemopreventive agent in **inflammation**-assocd. carcinogenesis.

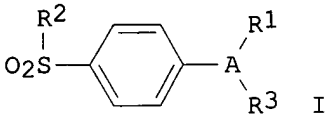
REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 8 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:84600 HCAPLUS
DOCUMENT NUMBER: 136:151161
TITLE: Preparation of 4-(heterocyclyl)benzenesulfonamides as components of a combination of a cyclooxygenase-2 inhibitors and a leukotriene B4 receptor antagonist
INVENTOR(S): Isakson, Peter C.; Anderson, Gary D.; Gregory, Susan A.
PATENT ASSIGNEE(S): G. D. Searle & Co., USA
SOURCE: U.S., 19 pp., Cont.-in-part of U.S. Ser. No.

489,415, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6342510	B1	20020129	US 1996-661641	19960611
CA 2224563	AA	19961227	CA 1996-2224563	19960611
US 2002107276	A1	20020808	US 2002-38080	20020103

PRIORITY APPLN. INFO.: US 1995-489415 B2 19950612
US 1996-661641 A1 19960611
OTHER SOURCE(S): MARPAT 136:151161
GI



I

AB The title compds. [I; A = (partially) unsatd. heterocyclyl or carbocyclyl; R1 = (un)substituted heterocyclyl, cycloalkyl, cycloalkenyl, aryl; R2 = Me, NH2; R3 = H, halo, alkyl, etc.] which are **cyclooxygenase-2** inhibitors used in combination with a **leukotriene B4** receptor antagonists for **treatment** of **inflammation** and **inflammation**-related disorders, were prepd. and formulated. Thus, **treating** Et trifluoroacetate with NaOMe in Me tert-Bu ether followed by addn. of 4'-chloroacetophenone (85%), and reacting the resulting 4,4,4-trifluoro-1-(4-chlorophenyl)butane-1,3-dione with 4-sulfonamidophenylhydrazine hydrochloride in EtOH afforded 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (80%).

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 9 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:56452 HCAPLUS
DOCUMENT NUMBER: 136:319028
TITLE: Anti-inflammatory activity of a novel selective cyclooxygenase-2 inhibitor, FR140423, on type II collagen-induced arthritis in Lewis rats
AUTHOR(S): Ochi, Takehiro; Goto, Toshio
CORPORATE SOURCE: Medicinal Biology Research Laboratories, Department of Immunology and Inflammation, Fujisawa Pharmaceutical Co., Ltd., Yodogawa-ku, Osaka, 532-8514, Japan
SOURCE: Prostaglandins & Other Lipid Mediators (2001), 66(4), 317-327
CODEN: POLMFL; ISSN: 1098-8823
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The mechanism of action of FR140423 (3-(difluoromethyl)-1-(4-methoxyphenyl)-5-[4-(methylsulfinyl)-phenyl]pyrazole), a novel and selective **cyclooxygenase (COX)-2** inhibitor, in rat type II collagen-induced arthritis was investigated and compared with that of indomethacin. We tested the inhibitory effects of FR140423 on paw edema and the formation of arachidonic acid metabolites in inflamed paws immunized with type II collagen. Oral administration of FR140423 showed a dose-dependent **anti-inflammatory** effect and was two-fold more potent than indomethacin. The increase of prostaglandin (PG) E2 and thromboxane (TX) B2 but not **leukotriene B4** in inflamed paws was assocd. with the development of paw edema. FR140423 and indomethacin dose-dependently suppressed the levels of PGE2 and TXB2 in arthritic rat paws. Unlike indomethacin, FR140423 did not induce gastric lesions in arthritic rats. These results suggest that FR140423 shows a potent **anti-inflammatory** effect mediated by inhibition of prostanoids produced by **COX-2** in inflamed tissues immunized with type II collagen, with a greatly improved safety profile compared to indomethacin.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 10 OF 39 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:5125 HCAPLUS

DOCUMENT NUMBER: 136:319026

TITLE: A pyrroloquinazoline derivative with anti-inflammatory and analgesic activity by dual inhibition of cyclo-oxygenase-2 and 5-lipoxygenase

AUTHOR(S): Rioja, Inmaculada; Terencio, M. Carmen; Ubeda, Amalia; Molina, Pedro; Tarraga, Alberto; Gonzalez-Tejero, Antonia; Alcaraz, M. Jose

CORPORATE SOURCE: Facultad de Farmacia, Departamento de Farmacologia, Universidad de Valencia, Burjasot, Valencia, 46100, Spain

SOURCE: European Journal of Pharmacology (2002), 434(3), 177-185
CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In a previous study, we reported a new pyrroloquinazoline deriv., 3-(4'-acetoxy-3',5'-dimethoxy)benzylidene-1,2-dihydropyrrolo[2,1-b]quinazoline-9-one (PQ), which inhibited human purified 5-lipoxygenase activity and prostaglandin E2 release in lipopolysaccharide-stimulated RAW 264.7 cells. In the present work, we show that PQ inhibits **cyclo-oxygenase-2** activity in intact cell assays (human monocytes) and purified enzyme prepns. (ovine isoenzymes) without affecting cyclo-oxygenase-1 activity. This behavior was confirmed in vivo by using the zymosan-injected mouse air pouch model, where PQ caused a marked redn. in cell migration and **leukotriene B4** levels at 4 h, as well as inhibition of prostaglandin E2 levels without affecting **cyclo-oxygenase-2** expression at 24 h after zymosan stimulation. In addn., oral

administration of this compd. significantly reduced carrageenan-induced mouse paw edema and phenyl-p-benzoquinone-induced writhings in mice. These results indicate that oral PQ exerts analgesic and **anti-inflammatory** effects, which are related to dual inhibition of **cyclo-oxygenase-2** and 5-lipoxygenase activities.

IT **71160-24-2, Leukotriene B4**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pyrroloquinazoline deriv. with **antiinflammatory** and analgesic activity by dual inhibition of **cyclooxygenase -2** and 5-lipoxygenase)

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 11 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:795108 HCAPLUS
DOCUMENT NUMBER: 136:144877
TITLE: Identification of Dual Cyclooxygenase-Eicosanoid Oxidoreductase Inhibitors: NSAIDs That Inhibit PG-LX Reductase/LTB4 Dehydrogenase
AUTHOR(S): Clish, Clary B.; Sun, Yee-Ping; Serhan, Charles N.
CORPORATE SOURCE: Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Biochemical and Biophysical Research Communications (2001), 288(4), 868-874
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Eicosanoids play key roles in many physiol. and disease processes, and their regulation by nonsteroidal **anti-inflammatory** drugs (NSAIDs) is crit. to many **therapeutic** approaches. These autacoids are rapidly inactivated by specific enzymes such as 15-hydroxyprostaglandin dehydrogenase (15-PGDH) and 15-oxoprostaglandin 13-reductase/ **leukotriene B4** 12-hydroxydehydrogenase (PGR/LTB4DH) that act on main series of eicosanoids (i.e., leukotrienes, prostaglandins), and recently found to act in lipoxin inactivation. Here, a panel of NSAIDs was assessed to det. each compd.'s ability to inhibit eicosanoid-directed activities of either the recombinant 15-PGDH or the PG-LXR/LTB4DH. The recombinant 15-PGDH that acts on both prostaglandin E2 (PGE2) and lipoxin A4 (LXA4) was not significantly inhibited by the NSAIDs tested. In contrast, several of the widely used NSAIDs were potent inhibitors of the PG-LXR/LTB4DH that metabolizes 15-oxo-PGE2, and LTB4 as well as 15-oxo-LXA4. Diclofenac and indomethacin each inhibited PG-LXR/LTB4DH-catalyzed conversion of 15-oxo-PGE2 to 13,14-dihydro-15-oxo-PGE2 by 70 and 95%, resp. Also, a **COX -2** inhibitor, niflumic acid, inhibited the PG-LXR/LTB4DH eicosanoid oxidoreductase (EOR) by 80% while other **COX-2** inhibitors such as nimesulide and **NS-398** did not inhibit this enzyme. These results indicate that certain clin. useful NSAIDs such as diclofenac and indomethacin, in addn. to

inhibiting **cyclooxygenases** (1 and **2**), also interfere with eicosanoid degrdn. by blocking PG-LXR/LTB4DH (EOR) and are members of a new class of dual cyclooxygenase (COX)-EOR inhibitors. Moreover, they suggest that the impact of NSAIDs on PG-LXR/LTB4DH activities as targets in the local tissue regulation of eicosanoid-mediated processes should be taken into account. (c) 2001 Academic Press.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 12 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:150965 HCAPLUS
DOCUMENT NUMBER: 135:286
TITLE: The anti-inflammatory effect of FR188582, a highly selective inhibitor of cyclooxygenase-2, with an ulcerogenic sparing effect in rats
AUTHOR(S): Ochi, Takehiro; Yamane-Sugiyama, Aiko; Ohkubo, Yoshitaka; Sakane, Kazuo; Tanaka, Hirokazu
CORPORATE SOURCE: Department of Immunology and Inflammation, Medicinal Biology Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., Osaka, 532-8514, Japan
SOURCE: Japanese Journal of Pharmacology (2001), 85(2), 175-182
CODEN: JJPAAZ; ISSN: 0021-5198
PUBLISHER: Japanese Pharmacological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **anti-inflammatory** and ulcerogenic effects of FR188582, 3-chloro-5-[4-(methylsulfonyl)phenyl]-1-phenyl-1H-pyrazole, were investigated. In a recombinant human cyclooxygenase (COX) enzyme activity, FR188582 inhibited **COX-2** with an IC50 value of 0.017 .mu.M, and the inhibition of prostaglandin (PG) E2 formation by FR188582 was over 6000 times more selective for **COX-2** than **COX**-1. Oral administration of FR188582 dose-dependently inhibited adjuvant arthritis. This effect was threefold more potent than that of indomethacin. FR188582 and indomethacin dose-dependently suppressed the formation of immunoreactive PGE2, but not immunoreactive **leukotriene B4**, in arthritic paw. Unlike indomethacin, FR188582 did not induce visible gastric lesions in rats at doses up to 32 mg/kg, p.o. Furthermore, FR188582 did not inhibit the level of immunoreactive PGE2 and immunoreactive 6-keto PGF1.alpha. in rat gastric mucosa. These results suggest that FR188582, a highly selective **COX-2** inhibitor, has a potent **anti-inflammatory** effect mediated by inhibition of PGE2 in inflamed tissues. The safety profile of FR188582 appears to be improved over the safety profile of indomethacin.

IT **71160-24-2, Leukotriene B4**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**anti-inflammatory** and ulcerogenic effect of FR188582, a **cyclooxygenase-2** inhibitor, in rats)

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE

IN THE RE FORMAT

L79 ANSWER 13 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:125444 HCAPLUS
DOCUMENT NUMBER: 134:294393
TITLE: Cloning, expression, and up-regulation of inducible rat prostaglandin E synthase during lipopolysaccharide-induced pyresis and adjuvant-induced arthritis
AUTHOR(S): Mancini, Joseph A.; Blood, Katherine; Guay, Jocelyne; Gordon, Robert; Claveau, David; Chan, Chi-Chung; Riendeau, Denis
CORPORATE SOURCE: Departments of Biochemistry and Molecular Biology, Merck Frosst Centre for Therapeutic Research, Kirkland, QC, H9R 4P8, Can.
SOURCE: Journal of Biological Chemistry (2001), 276(6), 4469-4475
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

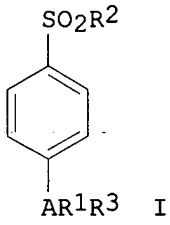
AB The authors have cloned and expressed the inducible form of prostaglandin (PG) E synthase from rat and characterized its regulation of expression in several tissues after in vivo lipopolysaccharide (LPS) challenge. The rat PGE synthase is 80% identical to the human enzyme at the amino acid level and catalyzes the conversion of PGH2 to PGE2 when overexpressed in Chinese hamster ovary K1 (CHO-K1) cells. PGE synthase activity was measured using [3H]PGH2 as substrate and stannous chloride to terminate the reaction and convert all unreacted unstable PGH2 to PGF2.alpha. before high pressure liq. chromatog. anal. The authors assessed the induction of PGE synthase in tissues from Harlan Sprague-Dawley rats after LPS-induced pyresis in vivo. Rat PGE synthase was up-regulated at the mRNA level in lung, colon, brain, heart, testis, spleen, and seminal vesicles. **Cyclooxygenase** (**COX**)**-2** and interleukin 1.beta. were also up-regulated in these tissues, although to different extents than PGE synthase. PGE synthase and **COX-2** were also up-regulated to the greatest extent in a rat model of adjuvant-induced arthritis. The RNA induction of PGE synthase in lung and the adjuvant-**treated** paw correlated with a 3.8- and 16-fold induction of protein seen in these tissues by immunoblot anal. Because PGE synthase is a member of the membrane-assocd. proteins in eicosanoid and glutathione metab. (MAPEG) family, of which leukotriene (LT) C4 synthase and 5-lipoxygenase-activating protein are also members, the authors tested the effect of LTC4 and the 5-lipoxygenase-activating protein inhibitor **MK-886** on PGE synthase activity. LTC4 and **MK-886** were found to inhibit the activity with IC50 values of 1.2 and 3.2 .mu.M, resp. The results demonstrate that PGE synthase is up-regulated in vivo after LPS or adjuvant administration and suggest that this is a key enzyme involved in the formation of PGE2 in **COX-2**-mediated **inflammatory** and pyretic responses.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 14 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:754502 HCAPLUS
DOCUMENT NUMBER: 133:321880
TITLE: Treatment of inflammation and inflammation-related disorders with a combination of a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor.
INVENTOR(S): Isakson, Peter C.; Anderson, Gary D.; Gregory, Susan A.
PATENT ASSIGNEE(S): G. D. Searle & Co., USA
SOURCE: U.S., 21 pp., Cont.-in-part of U.S. Ser. No. 489,472, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6136839	A	20001024	US 1996-661660	19960611
CA 2224517	AA	19961227	CA 1996-2224517	19960611

PRIORITY APPLN. INFO.: US 1995-489472 B2 19950612
OTHER SOURCE(S): MARPAT 133:321880
GI



I

AB A combination comprising a 5-lipoxygenase inhibitor and a cyclooxygenase-2 inhibitor selected from title compds. [I; A = pyrazolyl; R1 = .gtoreq.1 of (substituted) heterocyclyl, cycloalkyl, cycloalkenyl, aryl; R2 = Me, amino; R3 = H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, CO2H, cyanoalkyl, heterocyclyloxy, alkoxy, alkylthio, alkylcarbonyl, aryl, haloalkyl, etc.], is claimed. Thus, EtO2CCHF2 in MeOCMe3 was treated with NaOMe and then with 3-fluoro-4-methoxyacetophenone (prepn. given) followed by 16 h stirring to give 96% 4,4-difluoro-1-(3-fluoro-4-methoxyphenyl)butane-1,3-dione. This was refluxed 16 h with 4-sulfonamidophenylhydrazine hydrochloride in EtOH to give 87% 4-[5-(3-fluoro-4-methoxyphenyl)-3-difluoromethyl-1H-pyrazol-1-yl]benzenesulfonamide (II). II with 6-[[3-fluoro-5-(3,4,5,6-tetrahydro-4-methoxy-2H-pyran-4-yl)phenoxy]methyl]-1-methyl-1H-quinazolin-2-one (III) at 30 mpk/day orally in mice in the collagen-induced arthritis screen reduced incidence of arthritis to 20% (vs. 100% for controls). A formulation contg. II and III is given.
IT **93211-49-5, L 651392 101910-24-1**

, **PF 5901 110501-66-1, TMK**
688 111908-95-3, SK&F 104493 **118414-82-7**
, L 663536 **127378-46-5, CI 987**
132734-43-1, LY 233569
133430-69-0, ETH 615 147030-01-1
, **MK 591 147432-77-7,** Ontazolast
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**treatment** of **inflammation** and **inflammation**-related disorders with a combination of a **cyclooxygenase-2** inhibitor and a 5-lipoxygenase inhibitor)
REFERENCE COUNT: 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 15 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:743814 HCAPLUS
DOCUMENT NUMBER: 134:231778
TITLE: The cytotoxicity of chronic neuroinflammation upon basal forebrain cholinergic neurons of rats can be attenuated by glutamatergic antagonism or cyclooxygenase-2 inhibition
AUTHOR(S): Willard, L. B.; Hauss-Wegrzyniak, B.; Danysz, W.; Wenk, G. L.
CORPORATE SOURCE: Division of Neural Systems, Memory, and Aging, University of Arizona, Tucson, AZ, 85724, USA
SOURCE: Experimental Brain Research (2000), 134(1), 58-65
CODEN: EXBRAP; ISSN: 0014-4819
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The proinflammagen lipopolysaccharide (LPS) was infused chronically (37 days) into the basal forebrain of rats. Expts. then investigated whether the chronic administration of either a noncompetitive N-methyl-D-aspartate (NMDA)-sensitive receptor antagonist, memantine, or a selective cyclooxygenase-2/lipoxygenase inhibitor, CI987, could provide significant neuroprotection from the cytotoxic effects of LPS-induced neuroinflammation. Chronic LPS infusions decreased cortical choline acetyltransferase activity, which paralleled a decline in the no. of choline-acetyltransferase-immunoreactive cells within the basal forebrain as well as the no. of activated resident microglia. The infusions appeared to be selective for cholinergic neurons. Peripheral administration of memantine (i.p.) or CI987 (s.c.) attenuated the cytotoxic effects of the chronic inflammatory processes upon cholinergic cells within the basal forebrain. However, only CI987 attenuated the neuroinflammation produced by LPS and the subsequent changes in microglial activation. These results indicate that the cytotoxic effects of chronic neuroinflammation may involve prostanoid synthesis and may operate through NMDA receptors, and that the effects of prostaglandins occur upstream to NMDA-receptor activation.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 16 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:597692 HCAPLUS
DOCUMENT NUMBER: 133:261254
TITLE: Selenoorganic compound, ebselen, inhibits nitric oxide and tumor necrosis factor-.alpha. production by the modulation of jun-N-terminal kinase and the NF-.kappa.B signaling pathway in rat Kupffer cells
AUTHOR(S): Shimohashi, Naoya; Nakamuta, Makoto; Uchimura, Koutaro; Sugimoto, Rie; Iwamoto, Hiroaki; Enjoji, Munechika; Nawata, Hajime
CORPORATE SOURCE: Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, 812-8582, Japan
SOURCE: Journal of Cellular Biochemistry (2000), 78(4), 595-606
CODEN: JCEBD5; ISSN: 0730-2312
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In response to the bacterial endotoxin, LPS, Kupffer cells are induced to express NO and TNF-.alpha.. These compds. are involved in hepatic inflammation/injury, esp. that assocd. with endotoxic shock. In this study, we demonstrate that **ebselen** (2-phenyl-1,2-benzisoselenazol-3[2H]one), a selenoorg. compd., blocks LPS-induced NO and TNF-.alpha. prodn. by cultured rat liver Kupffer cells. LPS can activate both the NF-.kappa.B signaling pathway and MAPK signal transduction pathways such as JNK and p38 MAPK. We find that **ebselen** inhibits LPS-induced NF-.kappa.B nuclear trans-localization, and also suppresses the LPS-induced phosphorylation of JNK, but not the phosphorylation of p38 MAPK. This inhibition of signal transduction leads to a decrease in the transcription of TNF-.alpha. and the inducible isoform of NO. Furthermore, **ebselen** inhibits LPS-induced **COX-2** expression, which is responsible for proinflammatory prostaglandin prodn., without affecting constitutive COX-1 expression. These data suggest the mechanism by which **ebselen** acts as an **antiinflammatory** agent, and also suggest that **ebselen** may be potent in preventing hepatic injury such as endotoxic shock, in which Kupffer cell activation has been implicated.
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 17 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:507751 HCAPLUS
DOCUMENT NUMBER: 133:218084
TITLE: Cholesterol modulates vascular reactivity to endothelin-1 by stimulating a pro-inflammatory pathway
AUTHOR(S): Paris, Daniel; Town, Terrence; Humphrey, James; Yokota, Kiyoko; Mullan, Michael
CORPORATE SOURCE: Roskamp Institute, University of South Florida, Tampa, FL, 33613, USA
SOURCE: Biochemical and Biophysical Research Communications (2000), 274(2), 553-558

CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hypercholesterolemia (HC) is assocd. with coronary endothelial dysfunction and increased circulating levels of endothelin-1. The authors show that pre-**treatment** of intact rat aortic rings with cholesterol synergistically enhances the vasoconstriction induced by endothelin-1 suggesting that elevated levels of cholesterol may predispose to hypertension by modulating the vascular reactivity to endogenous vasoconstrictors. Moreover, the authors report that SB202190, a selective inhibitor of p38 MAPK, and PD98059 an inhibitor of MEK1/2 are able to abolish the vasoactive properties of cholesterol. **MK-886**, an inhibitor of 5-lipoxygenase is inefficient at blocking the vasoactive properties of cholesterol, whereas **NS-398**, a selective inhibitor of **cyclooxygenase-2** (**COX-2**) completely abolishes cholesterol-induced vasoconstriction. In intact rat aortae, cholesterol stimulates prostaglandin E2 and prostaglandin F2.alpha. prodn., an effect that can be completely prevented by inhibiting p38 MAPK, or **COX-2**. In vitro, cholesterol appears to stimulate a similar pro-**inflammatory** pathway in human cerebrovascular smooth muscle cells. Disruption of the MAPK/**COX-2** pathway may represent a valuable **therapy** to block the hypertension assocd. with HC, as well as the development of atherosclerosis. (c) 2000 Academic Press.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 18 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:378092 HCAPLUS
DOCUMENT NUMBER: 133:202776
TITLE: An anti-inflammatory ditriazine inhibiting leukocyte functions and expression of inducible nitric oxide synthase and cyclo-oxygenase-2
AUTHOR(S): Rioja, I.; Ubeda, A.; Terencio, M. C.; Guillen, I.; Riguera, R.; Quintela, J. M.; Peinador, C.; Gonzalez, L. M.; Alcaraz, M. J.
CORPORATE SOURCE: Facultad de Farmacia, Departamento de Farmacologia, Universidad de Valencia, Burjasot, Valencia, 46100, Spain
SOURCE: European Journal of Pharmacology (2000), 397(1), 207-217
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A ditriazine deriv. (4,10-dichloropyrido[5,6:4,5]thieno[3,2-d':3,2-d]-1,2,3-ditriazine (DTD)) inhibited neutrophil functions, including degranulation, superoxide generation, and **leukotriene B4** prodn., without any effect on 5-lipoxygenase activity. This compd. reduced nitric oxide (NO) and prostaglandin E2 prodn. in mouse peritoneal macrophages stimulated with lipopolysaccharide, whereas no influence on the activity of inducible NO synthase, **cyclooxygenase-2** or **cyclooxygenase**-1 was obsd. DTD significantly reduced mouse paw edema induced by

carrageenan and also markedly reduced NO and prostaglandin E2 levels in exudates from 24-h zymosan-stimulated mouse air pouch. Western blot anal. showed that DTD reduced the expression of inducible NO synthase and **cyclooxygenase-2**. Our results indicate that DTD exerts **anti-inflammatory** effects related to the inhibition of neutrophil functions and of NO and prostaglandin E2 prodn., which could be due to a decreased expression of inducible NO synthase and **cyclooxygenase-2**.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 19 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:147372 HCAPLUS
DOCUMENT NUMBER: 132:273659
TITLE: New anti-inflammatory treatment strategy in Alzheimer's disease
AUTHOR(S): Sugaya, Kiminobu; Uz, Tolga; Kumar, Vinod; Manev, Hari
CORPORATE SOURCE: The Psychiatric Institute, West Side VA Medical Center, Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, 60612, USA
SOURCE: Japanese Journal of Pharmacology (2000), 82(2), 85-94
CODEN: JJPAAZ; ISSN: 0021-5198
PUBLISHER: Japanese Pharmacological Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 111 refs. Numerous reports have indicated that patients suffering from **inflammatory** diseases (e.g., arthritis) who take **anti-inflammatory** medication have a reduced risk of developing Alzheimer's disease (AD). Thus, the first generation of **anti-inflammatory** cyclooxygenase (COX) inhibitors, such as aspirin and indomethacin, have been tested as potential **therapeutics** in AD. Because the inhibition of COX-1 is also known to cause tissue damage in the gastrointestinal system from the resultant reduced cytoprotection, selective **COX-2** inhibitors are being investigated and tested clin. as potentially better **therapeutics** for AD patients. However, such drugs may also trigger unwanted effects; for example, the **COX-2** inhibitors, which reduce the prodn. of one type of eicosanoids, the prostaglandins, may increase the prodn. of other eicosanoids; i.e., the **leukotriene B4** (LTB4), which is one of the most potent endogenous chemotactic/**inflammatory** factors. LTB4 prodn. is initiated by the enzyme 5-lipoxygenase (5-LOX). The expression of the 5-LOX gene is upregulated during neurodegeneration and with aging. In spite of the fact that 5-LOX and leukotrienes are major players in the **inflammation** cascade, their role in AD pathobiol./**therapy** has not been extensively investigated. We propose that the 5-LOX **inflammatory** cascade may take part in the process of aging-assocd. neurodegenerative diseases, and we point to the role of 5-LOX in neurodegeneration and discuss its relevance for **anti-inflammatory therapy** of AD.

REFERENCE COUNT: 111 THERE ARE 111 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE

IN THE RE FORMAT

L79 ANSWER 20 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:17557 HCAPLUS
DOCUMENT NUMBER: 132:160867
TITLE: Anti-inflammatory activity of macrolide antibiotics
AUTHOR(S): Ianaro, Angela; Ialenti, Armando; Maffia, Pasquale; Sautebin, Lidia; Rombola, Laura; Carnuccio, Rosa; Iuvone, Teresa; D'Acquisto, Fulvio; Di Rosa, Massimo
CORPORATE SOURCE: Department of Experimental Pharmacology, University of Naples "Federico II,", Naples, Italy
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2000), 292(1), 156-163
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of four macrolide antibiotics (roxithromycin, clarithromycin, erythromycin, and azithromycin) on the generation of some mediators and cytokines involved in the **inflammatory** process has been studied both in vivo and in vitro. Rat carrageenin pleurisy was used as a model of acute **inflammation**, and the macrolides were administered (10, 20, and 40 mg/kg p.o.) 1 h before the carrageenin challenge. Exudate vol. and leukocyte accumulation were both dose-dependently reduced by roxithromycin, clarithromycin and erythromycin in either normal or adrenalectomized animals. Furthermore, in normal rats, prostaglandin (PG)E2, nitrate plus nitrite, and tumor necrosis factor-.alpha. levels in pleural exudate were significantly reduced by these macrolides. Roxithromycin appeared more effective than erythromycin and clarithromycin, whereas azithromycin only slightly affected the **inflammatory** reaction. None of the macrolides were able to modify **leukotriene B4** exudate levels. In vitro expts. have shown that the four macrolides (5-80 .mu.M) reduced in a concn.-dependent manner the prodn. of 6-keto-PGF1.alpha., NO2-, tumor necrosis factor-.alpha., interleukin-1.beta., and interleukin-6 by lipopolysaccharide-stimulated J774 macrophages. In J774 cells, the inhibition of 6-keto-PGF1.alpha. and NO2- prodn. by roxithromycin and erythromycin was not dependent on direct inhibition of **cyclooxygenase-2** and inducible nitric oxide synthase activity because it appears to be related to the inhibition of **cyclooxygenase-2** and inducible nitric oxide synthase protein expression. In conclusion, the present study shows that macrolide antibiotics have **anti-inflammatory** activity, which likely depends on their ability to prevent the prodn. of pro-**inflammatory** mediators and cytokines, and suggest that these agents, particularly roxithromycin, can exert **therapeutic** effects independently of their antibacterial activity.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 21 OF 39 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:12866 HCAPLUS
DOCUMENT NUMBER: 132:73966
TITLE: Eicosanoid release in the endotoxin-primed isolated perfused rat lung and its pharmacological modification
AUTHOR(S): Amann, Rainer; Schuligoi, R.; Peskar, B. A.
CORPORATE SOURCE: Department Experimental Clinical Pharmacology, Univ. Graz, Graz, A-8010, Austria
SOURCE: Inflammation Research (1999), 48(12), 632-636
CODEN: INREFB; ISSN: 1023-3830
PUBLISHER: Birkhaeuser Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recent observations have demonstrated a central role of the "inducible" isoform of the **cyclooxygenase** (**COX**), **COX-2**, in the rat lung. Therefore, the reported capacity of selective **COX-2** inhibitors to potentiate the formation of leukotriene (LT) B, may raise concern about pro-**inflammatory** side effects of such drugs in the respiratory system. The present study was aimed at detg. the effects of the **COX-2** inhibitor **NS-398** on the release of COX and 5-lipoxygenase (LOX) metabolites of arachidonic acid in isolated perfused lungs obtained from endotoxin-**treated** rats before and after stimulation with the leukocyte secretagogues N-formyl-methionyl-leucyl-phenylalanine (FMLP). 2 H after rats had received endotoxin i.v., the lung was dissected and perfused via the pulmonary artery with physiol. salt soln. After an equilibration period of 20 min the outflow was collected (5-min fractions). In the resp. **treatment** groups, indomethacin, **NS-398**, or the 5-LOX inhibitor **MK886** were present throughout the expt., while FMLP was added to the perfusate during a single 5-min period. The concn. of eicosanoids in the outflow was detd. by RIA. Endotoxin **treatment** of rats resulted in increased expression of **COX-2** mRNA in lung tissue, and an elevated basal release of the prostaglandin (PG)I2 metabolite 6-keto PGE1.alpha., without a detectable increase of leukotriene (LT) formation. In vitro exposure to FMLP stimulated LT and prostanoid release, which was enhanced in endotoxin-primed lungs, and was suppressed by the 5-LOX inhibitor **MK-886** (3 .mu.M) and the COX-inhibitor indomethacin (5 .mu.M), resp. Either compd. showed selective inhibition of the resp. pathway of arachidonic acid metab. In endotoxin-primed lungs, the **COX-2** inhibitor **NS-398** (0.3-1.0 .mu.M) depressed basal as well as FMLP-stimulated release of 6-keto PGF1.alpha., but did not cause an increase of LTB4 or cysteinyl-LT release. These results suggest that FMLP, presumably acting on **inflammatory** cells trapped in the pulmonary circulation of endotoxin **treated** rats, induced prostanoid formation mainly via the **COX-2** pathway, and that its inhibition by **NS-398** had no detectable potentiating effect on LTB, or cysteinyl-LT biosynthesis.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 22 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:563787 HCAPLUS

DOCUMENT NUMBER: 131:193947
TITLE: New insights in the bronchodilatory and anti-inflammatory mechanisms of action of theophylline
AUTHOR(S): Juergens, Uwe R.; Degenhardt, Volker; Stober, Meinolf; Vetter, Hans
CORPORATE SOURCE: Dep. Pulmonary Diseases, Medical Policlinic, Univ. Bonn, Bonn, D-53111, Germany
SOURCE: Arzneimittel-Forschung (1999), 49(8), 694-698
CODEN: ARZNAD; ISSN: 0004-4172
PUBLISHER: Editio Cantor Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Phosphodiesterase (PDE) inhibition and adenosine antagonism were identified as important underlying mechanisms for the bronchodilating and **antiinflammatory** action of theophylline (CAS 58-55-9). The aim of the present study was to det. the effects of PDE inhibition by theophylline on cAMP and arachidonic acid (AA) metab., namely **leukotriene B4** (LTB4), and prostaglandin E2 (PGE2) prodn., in cultured monocytes in vitro. Monocytes obtained from healthy non-smoking subjects were incubated in adherence at 37.degree. for 4 h in the presence of theophylline (0.18, 1.8, and 18 .mu.g/mL, resp.) and stimulated with LPS (10 .mu.g/mL). LTB4, PGE, and cAMP were measured in the same culture supernatants by direct enzyme immunoassay. LPS-stimulated generation of cAMP increased (+162%) in the presence of theophylline (18 .mu.g/mL); prodn. of LTB4 was suppressed (-42%) compared to the baseline, whereas PGE2 prodn. increased (+39%). Prodn. of cAMP correlated with increased PGE2 prodn. and with suppression of LTB4. These effects were mimicked by cell permeant nucleotides, such as dibutyryl-cAMP but not by dibutyryl-cGMP and could be abolished by ibuprofen. These results provide the 1st evidence that the clin. efficacy of theophylline may result from inhibition of leukotriene prodn. and its capacity to stimulate PGE2 prodn. The underlying mechanism is suggested as feedback regulatory induction of **COX-2** by a prostaglandin driven cAMP-mediated process.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 23 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:507837 HCAPLUS
DOCUMENT NUMBER: 131:266744
TITLE: Local and systemic delivery of a stable aspirin-triggered lipoxin prevents neutrophil recruitment in vivo
AUTHOR(S): Clish, Clary B.; O'Brien, Jennifer A.; Gronert, Karsten; Stahl, Gregory L.; Petasis, Nicos A.; Serhan, Charles N.
CORPORATE SOURCE: Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1999), 96(14), 8247-8252

CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Aspirin (ASA) triggers a switch in the biosynthesis of lipid mediators, inhibiting prostanoid prodn. and initiating 15-epi-lipoxin generation through the acetylation of **cyclooxygenase II**. These aspirin-triggered lipoxins (ATL) may mediate some of ASA's beneficial actions and therefore are of interest in the search for novel **antiinflammatories** that could manifest fewer unwanted side effects. Here, we report that design modifications to native ATL structure prolong its biostability in vivo. In mouse whole blood, ATL analogs protected at carbon 15 [15(R/S)-methyl-lipoxin A4 (ATLa1)] and the omega end [15-epi-16-(para-fluoro)-phenoxy-LXA4 (ATLa2)] were recoverable to .apprxeq.90 and 100% at 3 h, resp., compared with a .apprxeq.40% loss of native lipoxin A4. ATLa2 retains bioactivity and, at levels as low as .apprxeq.24 nmol/mouse, potently inhibited tumor necrosis factor-.alpha.-induced leukocyte recruitment into the dorsal air pouch. Inhibition was evident by either local intra-air pouch delivery (.apprxeq.77% inhibition) or systemic delivery by i.v. injection (.apprxeq.85% inhibition) and proved more potent than local delivery of ASA. Rank order for inhibiting polymorphonuclear leukocyte infiltration was: ATLa2 (10 .mu.g, i.v.) .apprxeq.ATLa2 (10 .mu.g, local) .apprxeq.dexamethasone (10 .mu.g, local) >ASA (1.0 mg, local). Applied topically to mouse ear skin, ATLa2 also inhibited polymorphonuclear leukocyte infiltration induced by **leukotriene B4** (.apprxeq.78% inhibition) or phorbol ester (.apprxeq.49% inhibition), which initiates endogenous chemokine prodn. These results indicate that this fluorinated analog of natural aspirin-triggered lipoxin A4 is bioavailable by either local or systemic delivery routes and is a more potent and precise inhibitor of neutrophil accumulation than is ASA.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 24 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:744944 HCAPLUS
DOCUMENT NUMBER: 130:10625
TITLE: COX-2-selective carprofen and related compounds for treating pain and inflammation in dogs
INVENTOR(S): Lundy, Kristin Marie; Ricketts, Anthony Paul
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9850033	A1	19981112	WO 1998-IB662	19980501

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW,

MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9869321	A1	19981127	AU 1998-69321		19980501
EP 988034	A1	20000329	EP 1998-915041		19980501
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO					
BR 9808720	A	20000711	BR 1998-8720		19980501
JP 2000513020	T2	20001003	JP 1998-547869		19980501
NZ 500183	A	20020426	NZ 1998-500183		19980501
ZA 9803722	A	19991104	ZA 1998-3722		19980504
MX 9910148	A	20000228	MX 1999-10148		19991104
PRIORITY APPLN. INFO.:			US 1997-45635P	P	19970505
			WO 1998-IB662	W	19980501

OTHER SOURCE(S): MARPAT 130:10625

AB The invention relates to treating or preventing inflammatory processes and diseases in dogs assocd. with the activity of inducible cyclooxygenase-2 (COX-2), while at the same time reducing or eliminating undesirable side effects assocd. with simultaneous inhibition of the activity of constitutive cyclooxygenase-1 (COX-1) by selectively inhibiting COX-2 activity with ref. to COX-1 activity, wherein the selectivity ratio or COX-2:COX-1 activity inhibition is at least 3:1 based on ex vivo inhibition levels measured in whole blood. The inhibitor is a member selected from the group of antiinflammatory compds. consisting essentially of salicylic acid derivs., p-aminophenol derivs., indole and indene acetic acids, heteroaryl acetic acids, arylpropionic acids, anthranilic acids, enolic acids, and alkanones; the inhibitor in particular is comprised of the (+)(S)-enantiomer of 6-chloro-.alpha.-methyl-9H-carbazole-2-acetic acid.

IT **71160-24-2**, LTB4
RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitors; **COX-2**-selective carprofen and related compds. for **treating** pain and **inflammation** in dogs, and use with other agents)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 25 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:579441 HCAPLUS
DOCUMENT NUMBER: 129:310593
TITLE: Differential effects of inhibitors of cyclooxygenase (cyclooxygenase 1 and cyclooxygenase 2) in acute inflammation
AUTHOR(S): Gilroy, Derek W.; Tomlinson, Annette; Willoughby, Derek A.
CORPORATE SOURCE: William Harvey Research Institute, Department of Experimental Pathology, St. Bartholomew's and the Royal London School of Medicine and Dentistry, Charterhouse Square, London, EC1M 6BQ, UK
SOURCE: European Journal of Pharmacology (1998), 355(2/3), 211-217
CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **anti-inflammatory** activity of drugs more selective for cyclooxgenase isoform inhibition (**cyclooxygenase** 1, **cyclooxygenase 2**), were compared in rat carrageenin-induced pleurisy. Suppression of inflammation by **cyclooxygenase 2**-selective inhibitors, **NS-398** (N-[-2-cyclohexyloxy]-4-nitrophenyl methanesulfonamide) and nimesulide (4-nitro-2-phenoxy-methanesulfonanilide), and by piroxicam and aspirin, more selective for cyclooxygenase 1, was measured. Piroxicam and aspirin inhibited inflammatory cell influx, exudate and prostaglandin E2 formation, 6 h after carrageenin injection. **Cyclooxygenase 2** inhibitors had little effect on these parameters with **NS-398** alone reducing prostaglandin E2 levels, but increasing levels of **leukotriene B4**. In contrast, at 3 h after carrageenin injection, **cyclooxygenase 2** inhibitors significantly inhibited all inflammatory parameters however suppression with piroxicam and aspirin was greater, and more pronounced than at 6 h. **NS-398** and nimesulide dosing did not reduce thromboxane B2 prodn. from platelets isolated from rats with carrageenin-induced pleurisy, demonstrating that at the doses used, **cyclooxygenase 2** inhibitors did not inhibit cyclooxygenase 1, as platelets contain only this isoform. Therefore, in the rat carrageenin-induced pleurisy, drugs more selective for the inhibition of cyclooxygenase 1 attenuate inflammation over a wider time frame than **cyclooxygenase 2**-selective drugs, suggesting a significant role for cyclooxygenase 1 in this model. Inhibition of **cyclooxygenase 2** by **NS-398** however, resulted in an increase in the potent chemoattractant **leukotriene B4**.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 26 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:483336 HCAPLUS
DOCUMENT NUMBER: 129:298092
TITLE: Measurement of cyclooxygenase inhibition in vivo: a study of two non-steroidal anti-inflammatory drugs in sheep
AUTHOR(S): Cheng, Z.; Nolan, A. M.; Mckellar, Q. A.
CORPORATE SOURCE: Division of Veterinary Pharmacology, Department of Veterinary Preclinical Studies, University of Glasgow, Glasgow, G61 1QH, UK
SOURCE: Inflammation (New York) (1998), 22(4), 353-366
CODEN: INFLD4; ISSN: 0360-3997
PUBLISHER: Plenum Publishing Corp.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **anti-inflammatory** effects of the non-steroidal **anti-inflammatory** drugs phenylbutazone (PBZ) and flunixin meglumine (FM) and the relationship between the effects and drug concn. in vivo were studied using a s.c. tissue-cage model in sheep. Intracaveal injection of carrageenan induced prostaglandin (PG) E2 prodn. in

tissue-cage exudate (maximal concn., 101 nM) with significant increases in white blood cell (WBC) nos., skin temp. over the inflamed cage and exudate **leukotriene B4** (LTB4) concn. I.v. PBZ, 4.4 mg kg-1 produced mild inhibition of exudate PGE2 generation (10%), but greater inhibition of serum TXB2 (75.3%). The IC50 for TXB2 was 36.0 .mu.M. Phenylbutazone did not alter effects on skin temp., WBC nos. or exudate LTB4 concns. I.v. FM, 1.1 mg kg-1, inhibited carrageenan-induced exudate PGE2 formation (Emax, 100%, IC50, <0.4 nM) and serum TXB2 generation (Emax, 100%, IC50, 17 nM) for up to 32 h. Flunixin meglumine significantly inhibited the rise in skin temp. but had a limited effect on exudate WBC. Phenylbutazone and FM have distinct effects on carrageenan-induced **cyclooxygenase** (**COX-2**) and platelet **COX** (COX-1). Flunixin meglumine was a more potent COX inhibitor than PBZ and was more selective for the inducible form of COX in vivo.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 27 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:456107 HCAPLUS
DOCUMENT NUMBER: 129:184559
TITLE: Inhibition of inducible nitric oxide synthase by peroxisome proliferator-activated receptor agonists; correlation with induction of heme oxygenase 1
AUTHOR(S): Colville-Nash, Paul R.; Qureshi, Saima S.; Willis, Dean; Willoughby, Derek A.
CORPORATE SOURCE: Dep. of Experimental Pathology, St. Bartholomew's and Royal London School of Medicine and Dentistry, London, EC1 M 6BQ, UK
SOURCE: Journal of Immunology (1998), 161(2), 978-984
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Genetic knock-out in mice of peroxisome proliferator-activated receptor-.alpha. (PPAR.alpha.) can prolong **inflammation** in response to **leukotriene B4**. Although **cyclooxygenase 2** has been shown to be induced by PPAR activation, the effect of PPAR agonists on the key **inflammatory** enzyme systems of nitric oxide synthase (NOS) and stress proteins has not been investigated. The effect on these of naturally occurring eicosanoid PPAR agonists (**leukotriene B4** and 8(S)-hydroxyeicosatetraenoic acid, which are PPAR.alpha. selective; PGA2, PGD2, PGJ2, and .DELTA.12PGJ2, which are PPAR.gamma. selective) and the synthetic PPAR.alpha. agonist Wy14,643 was examd. in activated RAW264.7 murine macrophages. **Leukotriene B4** and 8(S)-hydroxyeicosatetraenoic acid stimulated nitrite accumulation, indicative of enhanced NOS activity. PGA2, PGD2, PGJ2, .DELTA.12PGJ2, Wy14,643 reduced nitrite accumulation, with .DELTA.12PGJ2 being the most effective. The mechanism behind this redn. was examd. using Western blotting. Inhibition of nitrite accumulation was assocd. with a fall in inducible NOS protein and an induction of heme oxygenase 1, correlating both dose dependently and temporally. Other proteins examd. (**cyclooxygenase 2**, heme oxygenase 2, heat

shock protein 70, and glucose-regulated protein 78) were unaffected. The data suggest that naturally occurring PPAR agonists can inhibit the inducible NOS enzyme pathway. This inhibition may be mediated by modulation of the stress protein, heme oxygenase 1. Thus, the generation of eicosanoid breakdown products during **inflammation** may contribute to its eventual resoln. by activation of the PPAR system. This system may thus represent a novel target for **therapeutic** intervention in **inflammatory** disease.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 28 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:366976 HCAPLUS
DOCUMENT NUMBER: 129:157253
TITLE: The role of cyclooxygenase-1 and cyclooxygenase-2 in lipopolysaccharide and interleukin-1 stimulated enterocyte prostanoid formation
AUTHOR(S): Longo, W. E.; Damore, L. J.; Mazuski, J. E.; Smith, G. S.; Panesar, N.; Kaminski, D. L.
CORPORATE SOURCE: Department of Surgery, Theodore Cooper Surgical Research Institute, St Louis University School of Medicine and Health Sciences Center, St Louis, MO, 63110-0250, USA
SOURCE: Mediators of Inflammation (1998), 7(2), 85-91
CODEN: MNFLEF; ISSN: 0962-9351
PUBLISHER: Carfax Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Lipopolysaccharide is an **inflammatory** agent and interleukin-1 is a cytokine. Their pro-**inflammatory** effects may be mediated by prostanoids produced by inducible **cyclooxygenase-2**. The aim of this study was to det. the prostanoids produced by lipopolysaccharide and interleukin-1 stimulated enterocytes through the **cyclooxygenase**-1 and **2** pathways. Cultured enterocytes were stimulated with lipopolysaccharide or interleukin-1.beta. with and without cyclooxygenase inhibitors. Low concns. of indomethacin and valerylsalicylic acid (VSA) were evaluated as cyclooxygenase-1 inhibitors and their effects compared with the effects of a specific **cyclooxygenase-2** inhibitor, SC-58125. Prostaglandin E2, 6-keto prostaglandin F1.alpha., prostaglandin D2 and **leukotriene B4** levels were detd. by RIA. Immunoblot anal. using isoform-specific antibodies showed that the inducible **cyclooxygenase** enzyme (**COX-2**) was expressed by 4 h in LPS and IL-1.beta. **treated** cells while the constitutive COX-1 remained unaltered in its expression. Interleukin-1.beta. and lipopolysaccharide stimulated the formation of all prostanoids compared with untreated cells, but failed to stimulate **leukotriene B4**. Indomethacin at 20 .mu.M concn., and VSA inhibited lipopolysaccharide and interleukin 1.beta. stimulated prostaglandin E2, but not 6-keto prostaglandin F1.alpha. formation. SC-58125 inhibited lipopolysaccharide and interleukin-1.beta. stimulated 6-keto prostaglandin F1.alpha. but not prostaglandin E2 release. The specific **cyclooxygenase**

-2 inhibitor also inhibited lipopolysaccharide produced prostaglandin D2 but not interleukin-1.beta. stimulated prostaglandin D2. While SC-58125 inhibited basal 6-keto prostaglandin-F1.alpha. formation it significantly increased basal prostaglandin E2 and prostaglandin D2 formation. As SC-58125 inhibited lipopolysaccharide and interleukin-1.beta. induced 6-keto prostaglandin F1.alpha. prodn. but not prostaglandin E2 prodn., it suggests that these agents stimulate prostacyclin prodn. through a **cyclooxygenase-2** mediated mechanism and prostaglandin E2 prodn. occurs through a cyclooxygenase-1 mediated mechanism. Prostaglandin D2 prodn. appeared to be variably produced by cyclooxygenase-1 or **cyclooxygenase-2**, depending on the stimulus.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L79 ANSWER 29 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:557660 HCAPLUS
DOCUMENT NUMBER: 127:239120
TITLE: Compositions comprising a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist for reducing transplant rejection
INVENTOR(S): Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary
PATENT ASSIGNEE(S): G.D. Searle & Co., USA; Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9729775	A1	19970821	WO 1997-US1422	19970211
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2246356	AA	19970821	CA 1997-2246356	19970211
AU 9722500	A1	19970902	AU 1997-22500	19970211
EP 880362	A1	19981202	EP 1997-905663	19970211
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2000505445	T2	20000509	JP 1997-529359	19970211
US 6172096	B1	20010109	US 1998-75633	19980511

PRIORITY APPLN. INFO.: US 1996-600580 A1 19960213
WO 1997-US1422 W 19970211
OTHER SOURCE(S): MARPAT 127:239120

AB Treatment with a cyclooxygenase-2 inhibitor and a leukotriene B4 receptor antagonist is described as being useful in reducing recipient rejection of transplanted organs and for treatment of

autoimmune diseases.

L79 ANSWER 30 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:530509 HCAPLUS
DOCUMENT NUMBER: 127:229352
TITLE: Evaluation of the anti-inflammatory activity of a dual cyclooxygenase-2 selective/5-lipoxygenase inhibitor, RWJ 63556, in a canine model of inflammation
AUTHOR(S): Kirchner, T.; Argentieri, D. C.; Barbone, A. G.; Singer, M.; Steber, M.; Ansell, J.; Beers, S. A.; Wachter, M. P.; Wu, W.; Malloy, E.; Stewart, A.; Ritchie, D. M.
CORPORATE SOURCE: The R.W. Johnson Pharmaceutical Research Institute, Raritan, NJ, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1997), 282(2), 1094-1101
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Sterile perforated polyethylene spheres (wiffle golf balls) were implanted s.c. in beagle dogs. A local **inflammatory** reaction was elicited within the spheres by injecting carrageenan. Changes in leukocyte count, prostaglandin E2, thromboxane B2 and **leukotriene B4** levels were monitored in fluid samples collected over a 24-h period. Blood samples were also collected at various time points and analyzed for prostaglandin E2 and **leukotriene B4** prodn. after ex vivo calcium ionophore **treatment**. Effects of std. **anti-inflammatory** agents (aspirin, indomethacin, dexamethasone, tenidap and zileuton) and newer **cyclooxygenase-2** (**COX-2**) selective agents (nimesulide, nabumetone and SC-58125) were detd. after oral administration. Ex vivo inhibition of cyclooxygenase product synthesis (prostaglandin E2, thromboxane B2) in whole blood was used as an indicator of activity for the constitutive COX-1 isoform, although inhibition of the synthesis of these mediators in the chamber exudate during an **inflammatory** process is believed to represent **COX-2** inhibition. **Treatment** effects on **leukotriene B4** prodn. were also detd. both ex vivo in whole blood and in the fluid. All of the compds. tested, except aspirin, inhibited leukocyte infiltration into the fluid exudate. Inhibitors that exert their effects on both isoenzymes of cyclooxygenase attenuate prodn. of cyclooxygenase metabolites in both the **inflammatory** exudate and in peripheral blood ex vivo, although **COX-2** selective inhibitors only demonstrated activity in the exudate. A 5-lipoxygenase inhibitor (zileuton), a corticosteroid (dexamethasone) and a dual **COX-2** selective/5-lipoxygenase inhibitor (RWJ 63556) had similar profiles in that they all inhibited cell infiltration and eicosanoid prodn. in the fluid and also attenuated **leukotriene B4** prodn. in both the fluid and blood.

IT **71160-24-2, Leukotriene B4**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**antiinflammatory** activity of **cyclooxygenase-2** selective/5-lipoxygenase inhibitor, RWJ 63556, in

canine model of inflammation)

L79 ANSWER 31 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:457355 HCAPLUS
DOCUMENT NUMBER: 127:171252
TITLE: Variabilin: A dual inhibitor of human secretory and cytosolic phospholipase A2 with anti-inflammatory activity
AUTHOR(S): Escrig, V.; Ubeda, A.; Ferrandiz, M. L.; Darias, J.; Sanchez, J. M.; Alcaraz, M. J.; Paya, M.
CORPORATE SOURCE: Dep. of Pharmacology, University of Valencia and Institute of Natural Products and Agrobiology, Tenerife, 46100, Spain
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1997), 282(1), 123-131
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The marine product variabilin was identified as a novel inhibitor of phospholipase A2 (PLA2), which exhibited IC50 values of 6.9 .mu.M and 7.9 .mu.M for human synovial secretory PLA2 an U937 cells cytosolic PLA2 activities, resp. This compd. was less potent on bee venom or zymosan-injected rat air pouch enzymes and failed to affect Naja naja venom PLA2. The prodn. of **leukotriene B4** by human neutrophils stimulated with calcium ionophore A23187 was also inhibited by variabilin, which was without effect on 5-lipoxygenase, cyclo-oxygenase 1 and **cyclo-oxygenase 2** activities in cell-free assays. Other functions of human neutrophils, such as degranulation and superoxide generation, were also significantly reduced in vitro. Variabilin administered topically suppressed the mouse ear edema induced by 12-O-tetradecanoylphorbol 13-acetate, whereas the ear edema induced by arachidonic acid was unaffected; this suggests an action previous to arachidonic acid metab. This compd. administered p.o. at 30 mg/kg and 45 mg/kg significantly inhibited mouse paw edema induced by carrageenan and, at 0.01 to 1.0 .mu.mol/pouch in the mouse air pouch injected with zymosan, exerted a marked inhibition on PGE2 and **leukotriene B4** levels in exudates (ID50 values of approx. 0.028-0.029 .mu.mol/pouch), without affecting cell migration. Our results indicate that variabilin is an inhibitor of human secretory and cytosolic PLA2 activities that controls eicosanoid prodn. in vitro and in vivo, inhibits neutrophil degranulation and superoxide generation in vitro and shows **anti-inflammatory** activity after topical or p.o. administration to mice.

L79 ANSWER 32 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:455060 HCAPLUS
TITLE: Patent evaluation
AUTHOR(S): Anon.
SOURCE: Expert Opinion on Therapeutic Patents (1997), 7(7), 765-771
CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal; Miscellaneous
LANGUAGE: English
AB This patent describes administration of several fixed combinations

of a selective **cyclooxygenase-2** inhibitor with a **leukotriene B4** receptor antagonist for the **treatment** of **inflammatory** diseases.

L79 ANSWER 33 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:305806 HCAPLUS
DOCUMENT NUMBER: 127:16402
TITLE: Nitric oxide synthase and cyclo-oxygenase pathways in the inflammatory response induced by zymosan in the rat air pouch
AUTHOR(S): Paya, Miguel; Pastor, Pablo Garcia; Coloma, Julio; Alcaraz, M. Jose
CORPORATE SOURCE: Departamento de Farmacologia, Facultad de Farmacia, Universidad de Valencia, Burjassot, 46100, Spain
SOURCE: British Journal of Pharmacology (1997), 120(8), 1445-1452
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have studied the participation of nitric oxide (NO) in an animal model of **inflammation**, the rat air pouch stimulated with zymosan. Saline or zymosan was injected into 6-day rat air pouches at different time points and measurements were made of cell migration, levels of nitrite/nitrate (NO2-/NO3-), prostaglandin E2 (PGE2), **leukotriene B4** (LTB4) and secretory phospholipase A2 (sPLA2) in exudates. Nitric oxide synthase (NOS) activity was detd. in high speed supernatants from cells present in pouch exudates. Western blot anal. was also performed on these samples. Zymosan injection induced a time-dependent increase in leukocyte infiltration, NO2-/NO3- levels and cellular NOS activity that reached a peak by 8 h. Western blot anal. showed the same time course for induction of NOS protein. Colchicine administration to rats inhibited cellular infiltration and decreased the levels of NO metabolites and cellular NOS activity zymosan-injected air pouch at 8 h. NOS activity was present in polymorphonuclear leukocytes (PMNs) and monocytes, but not in the lymphocytes present in exudates. This enzyme is calcium-independent and needs NADPH for activity. PGE2 levels in exudates showed a time course inverse to that of NOS activity and NO metabolites, with max. levels of PGE2 obsd. at 4 h after zymosan injection. Administration of NG-nitro-L-arginine Me ester (L-NAME) or aminoguanidine to rats significantly reduced cellular NOS activity, NO2-/NO3- levels and chemiluminescence, whereas they were without effect on cell migration and degranulation, eicosanoid levels and sPLA2 activity. **Treatment** of animals with dexamethasone inhibited cellular NOS activity, NO2-/NO3- levels, chemiluminescence and the increase in the levels of PGE2 and LTB4, with only a weak effect on elastase release. Administration of the selective **cyclo-oxygenase-2** (**COX-2**) inhibitor **NS398** to rats strongly reduced PGE2 levels in exudates without affecting NO metabolites or NOS activity at 4 h after zymosan injection. The authors' data indicate that NOS is induced in the zymosan-stimulated rat air pouch model of **inflammation**. This enzyme is expressed in the cells migrating into the air pouch and caused an increased prodn. of NO metabolites in exudates. The results also suggest the presence of

an earlier phase in which eicosanoids play the main role, with participation of **COX-2** activity, and a later phase mediated by NO. The endogenous release of NO does not modify prostaglandin biosynthesis in this in vivo model.

L79 ANSWER 34 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:175052 HCAPLUS
DOCUMENT NUMBER: 126:166481
TITLE: Combination of a **cyclooxygenase-2** inhibitor and a **leukotriene B4** receptor antagonist for the **treatment** of **inflammations**
INVENTOR(S): Isakson, Peter C.; Anderson, Gary D.; Gregory, Susan A.
PATENT ASSIGNEE(S): G.D. Searle & Co., USA
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9641645	A1	19961227	WO 1996-US9905	19960611
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
CA 2224563	AA	19961227	CA 1996-2224563	19960611
AU 9662694	A1	19970109	AU 1996-62694	19960611
EP 833664	A1	19980408	EP 1996-921477	19960611
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 11507669	T2	19990706	JP 1996-503237	19960611

PRIORITY APPLN. INFO.: US 1995-489415 A 19950612
WO 1996-US9905 W 19960611

OTHER SOURCE(S): MARPAT 126:166481

AB Combinations of a **cyclooxygenase-2** inhibitor and a **leukotriene B4** receptor antagonist are described for **treatment** of **inflammation** and **inflammation**-related disorders. The **cyclooxygenase-2** inhibitors were prepd. Also, formulations for the drug combination are described.

IT **32222-06-3, Calcitriol 60940-34-3, Ebselen 71125-38-7, Meloxicam 85259-71-8, Bay 0-8276 93211-49-5, L-651392 101910-24-1, PF 5901 110501-66-1, TMK-688 111908-95-3, SKF-104493 117423-74-2, LY 223982 117423-95-7, LY 213024 117690-79-6, LY 255283 118414-82-7, MK-886 119261-58-4, TEI 1338 120072-59-5, SC-**

41930 123653-11-2, NS-398
127378-46-5, CI 987 132734-43-1
, LY 233569 133430-69-0, ETH
-615 134578-96-4, ONO-4057
135199-82-5, LY 264086
135893-33-3, PF 10042
136326-31-3, WAY 121006
141059-52-1, SC-51146
141748-00-7, RP 69698
141835-49-6, RG 14893
142422-79-5, RP 66153
146461-98-5, SM 15178
147030-01-1, MK-591 147398-01-4
, CGS-25019C 147432-77-7, BI
-RM-270 150399-22-7, SB-
201993 153034-77-6, LY 292728
153633-01-3, SC 53228
158081-99-3, Pfizer 105696
161172-51-6, LY-293111
162011-90-7, MK 966 180208-37-1
, SB-201146 186912-76-5, L
752860 186912-79-8, LY 210073
186912-85-6, ONO-LB 448
186912-92-5, RP 66364
186912-94-7, SC 50505
187112-24-9, Floculide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of a **cyclooxygenase-2** inhibitor and a **leukotriene B4** receptor antagonist for **treatment** of **inflammation**)

L79 ANSWER 35 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:174992 HCAPLUS
DOCUMENT NUMBER: 126:166479
TITLE: Compositions comprising a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor for treatment of inflammation and inflammation-related disorders
INVENTOR(S): Isakson, Peter C.; Anderson, Gary D.; Gregory, Susan A.
PATENT ASSIGNEE(S): G.D. Searle and Co., USA
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9641626	A1	19961227	WO 1996-US10106	19960611

W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB,

GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN

CA 2224517	AA	19961227	CA 1996-2224517	19960611
AU 9661117	A1	19970109	AU 1996-61117	19960611
EP 833622	A1	19980408	EP 1996-918465	19960611
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 11507670	T2	19990706	JP 1997-503273	19960611

PRIORITY APPLN. INFO.: US 1995-489472 A 19950612
WO 1996-US10106 W 19960611

OTHER SOURCE(S): MARPAT 126:166479

AB Combinations of a cyclooxygenase-2 inhibitor and a 5-lipoxygenase inhibitor are described for treatment of inflammation and inflammation-related disorders. Prepn. of e.g. 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide is described., as are pharmaceutical formulations and activity against collagen-induced arthritis in mice.

IT **93211-49-5, L-651392 101910-24-1**, **PF-5901 110501-66-1, TMK-688 111908-95-3**, SK&F-104493 **118414-82-7**, L 663536 **127378-46-5, CI 987 132734-43-1, LY-233569 133430-69-0, ETH-615 147030-01-1**, **MK-591 147432-77-7**, Ontazolast
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**cyclooxygenase-2** inhibitor combination with 5-lipoxygenase inhibitor for **treatment** of **inflammation** and **inflammation**-related disorders, compd. prepn., antiarthritic activity and pharmaceutical compns.)

L79 ANSWER 36 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:657457 HCAPLUS
DOCUMENT NUMBER: 125:292089
TITLE: Pharmacology of meloxicam, a new non-steroidal anti-inflammatory drug with an improved safety profile through preferential inhibition of COX-2
AUTHOR(S): Engelhardt, G.
CORPORATE SOURCE: Department Biological Research, Dr Karl Thomae GmbH, Biberach, D-88400, Germany
SOURCE: British Journal of Rheumatology (1996), 35(Suppl. 1), 4-12
CODEN: BJRHDF; ISSN: 0263-7103
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 69 refs. is presented on key pharmacol. findings of a new non-steroidal **anti-inflammatory** drug (NSAID), **meloxicam**. Unlike established NSAIDs, **meloxicam** preferentially inhibits inducible **COX-2** in guinea-pig peritoneal macrophages and human **COX-2** in COS cells. Compared with other NSAIDs, **meloxicam** is the most potent inhibitor of prostaglandin biosynthesis in pleural and peritoneal exudate, but only a weak inhibitor in the gastric tract and kidney. Ulcerogenicity in the rat stomach is weak in relation to **anti-inflammatory** potency, resulting in a high **therapeutic** index. **Meloxicam**'s high **anti**

-**inflammatory** potency combined with good tolerability can be explained by its preferential inhibition of **COX-2**. In adjuvant arthritis rats, **meloxicam** inhibits not only paw swelling, but also bone and cartilage destruction and systemic signs of disease. It inhibits leukocyte migration, but has no effect on **leukotriene B4** or C4. **Meloxicam** shows a long-lasting **anti-inflammatory** and analgesic effect on **inflammatory** pain and reduces pyrogen-induced fever, but has no central nervous system effects. The pharmacokinetic profile of **meloxicam** in the rat is similar to that in man. Metabolites are inactive.

L79 ANSWER 37 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:607824 HCAPLUS
DOCUMENT NUMBER: 125:237992
TITLE: Leukocyte lipid body formation and eicosanoid generation: cyclooxygenase-independent inhibition by aspirin
AUTHOR(S): Bozza, Patricia T.; Payne, Jennifer L.; Morham, Scott G.; Langenbach, Robert; Smithies, Oliver; Weller, Peter F.
CORPORATE SOURCE: Harvard Thorndike Laboratory, Harvard Medical School, Boston, MA, 02215-5491, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1996), 93(20), 11091-11096
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Lipid bodies, cytoplasmic inclusions that develop in cells assocd. with inflammation, are inducible structures that might participate in generating inflammatory eicosanoids. Cis-unsatd. fatty acids (arachidonic and oleic acids) rapidly induced lipid body formation in leukocytes, and this lipid body induction was inhibited by aspirin and nonsteroidal **antiinflammatory** drugs (NSAIDs). Several findings indicated that the inhibitory effect of aspirin and NSAIDs on lipid body formation was independent of cyclooxygenase (COX) inhibition. First, the non-COX inhibitor, sodium salicylate, was as potent as aspirin in inhibiting lipid body formation elicited by cis-fatty acids. Second, cis-fatty acid-induced lipid body formation was not impaired in macrophages from COX-1 or **COX-2** genetically deficient mice. Finally, NSAIDs inhibited arachidonic acid-induced lipid body formation likewise in macrophages from wild-type and COX-1- and **COX-2**-deficient mice. An enhanced capacity to generate eicosanoids developed after 1 h concordantly with cis-fatty acid-induced lipid body formation. Arachidonic and oleic acid-induced lipid nos. correlated with the enhanced levels of **leukotrienes B4** and C4 and prostaglandin E2 produced after submaximal calcium ionophore stimulation. Aspirin and NSAIDs inhibited both induced lipid body formation and the enhanced capacity for forming leukotrienes as well as prostaglandins. Our indicate that lipid body formation is an inducible early response in leukocytes that correlates with enhanced eicosanoid synthesis. Aspirin and NSAIDs, independent of COX inhibition, inhibit cis-fatty acid-induced lipid body formation in leukocytes and in concert inhibit the enhanced synthesis of leukotrienes and prostaglandins.

L79 ANSWER 38 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:566543 HCAPLUS
DOCUMENT NUMBER: 125:316578
TITLE: Inhibition of inflammatory responses by a series of novel dolabrane derivatives
AUTHOR(S): Paya, Miguel; Ferrandiz, Maria Luisa; Erradi, Fatima; Terencio, Maria Carmen; Kijjoa, Anake; Pinto, Madalena M. M.; Alcaraz, Maria Jose
CORPORATE SOURCE: Departamento de Farmacologia, Universidad de Valencia, Facultad de Farmacia, Av. Vicent Andres Estelles s/n, 46100, Burjassot, Spain
SOURCE: European Journal of Pharmacology (1996), 312(1), 97-105
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Four dolabrane derivs. isolated from Endospermum diadenum have been studied for their inhibitory effects on murine models of inflammation and human neutrophil functions in vitro. After topical application, akendo 1, akendo 2 and akendo 3 potently inhibited the mouse ear edema induced by 12-O-tetradecanoylphorbol acetate (TPA) with a striking effect on myeloperoxidase levels. After oral administration, akendo 2 and akendo 3 inhibited mouse paw edema induced by carrageenan, with a significant redn. in myeloperoxidase levels. In contrast to indomethacin, they did not modify the prostaglandin E2 content of the inflamed paw. None of the compds. affected superoxide generation by human neutrophils. On the contrary, they inhibited degranulation induced by different stimuli. The most effective compds. were akendo 2 and akendo 3, which also inhibited myeloperoxidase activity. All compds. were weak inhibitors of **leukotriene B4** synthesis and release by human neutrophils, whereas only akendo 3 decreased 5-lipoxygenase activity. Cyclo-oxygenase-1 from human platelets was inhibited mainly by akendo 2 and akendo 3, although with a low potency. The latter compd. also reduced weakly the synthesis of prostaglandin E2 by **cyclo-oxygenase-2**. The **anti-inflammatory** activity of these dolabrane derivs. was not related to arachidonic acid mobilization or metab.

L79 ANSWER 39 OF 39 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:12558 HCAPLUS
DOCUMENT NUMBER: 124:105962
TITLE: Meloxicam. Part II. In vivo findings
AUTHOR(S): Engelhardt, G.; Boegel, R.; Schnitzler, Chr.; Utzmann, R.
CORPORATE SOURCE: Department Pharmacological Research, Dr. Karl Thomae GMBH, Biberach/Riss, D-88397, Germany
SOURCE: Biochemical Pharmacology (1996), 51(1), 29-38
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Meloxicam** is a new nonsteroidal **anti-inflammatory** drug (NSAID) derived from enolic acid. Preclin. studies have indicated that **meloxicam** has potent

anti-inflammatory activity, together with a good gastrointestinal and renal tolerability profile. This report summarizes studies undertaken to compare **meloxicam** to other NSAIDs in the inhibition of the inducible **cyclooxygenase** (**COX-2**) in inflamed areas (pleurisy of the rat, peritonitis of mice) and their influence on the activity of the constitutive cyclooxygenase (COX-1) in stomach, kidney, brain, and blood. In pleurisy of the rat, **meloxicam** was twice as potent as tenoxicam, 3 times as potent as flurbiprofen, 8 times as potent as diclofenac, and 20 times as potent as tenidap at inhibiting prostaglandin E2 (PGE2) biosynthesis. In the peritonitis model in mice, **meloxicam** was approx. twice as active as piroxicam, and more than 10 times as active as diclofenac in the suppression of PGE biosynthesis. Doses of **meloxicam** sufficient to inhibit PGE2 biosynthesis in the pleural exudate and peritoneal exudate had no influence on **leukotriene-B4** (LTB4) or leukotriene-C4 (LTC4) content. The effect of **meloxicam** on the PGE2 content of rat gastric juice and rat urine was weaker than that of piroxicam or diclofenac. **Meloxicam** was a weaker inhibitor of the increased PGE2 concn. in brain of rats and mice (induced by convulsant doses of pentetrazole) than piroxicam, diclofenac, or indomethacin. **Meloxicam** had a weaker effect on serum thromboxane-B2 (TXB2) concn. in rats than piroxicam or tenoxicam. The in vivo findings confirm the results of in vitro tests, conducted sep., showing that **meloxicam** preferentially inhibits **COX-2** over **COX-1**. **COX-2** is the inducible isoenzyme implicated in the inflammatory response, whereas COX-1 has cytoprotective effects in the gastric mucosa. Therefore, a preferential selectivity for one isoenzyme over another, as displayed by **meloxicam**, may have implications in the clin. setting in terms of a more favorable risk: benefit profile.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 16:04:34 ON 11 JUN 2003)

L80 54 S L75
L81 60 S L77
L82 97 S L80 OR L81
L83 41 DUP REM L82 (56 DUPLICATES REMOVED)

L83 ANSWER 1 OF 41 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2003177056 IN-PROCESS
DOCUMENT NUMBER: 22581829 PubMed ID: 12694395
TITLE: Valproic acid down-regulates the conversion of arachidonic acid to eicosanoids via cyclooxygenase-1 and -2 in rat brain.
AUTHOR: Bosetti Francesca; Weerasinghe Gayani R; Rosenberger Thad A; Rapoport Stanley I
CORPORATE SOURCE: Brain Physiology and Metabolism Section, National Institute on Aging, National Institutes of Health, Bethesda, Maryland, USA.
SOURCE: JOURNAL OF NEUROCHEMISTRY, (2003 May) 85 (3) 690-6. Journal code: 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030417

Last Updated on STN: 20030417

AB Sodium valproate, a mood stabilizer, when chronically administered to rats (200 mg/kg i.p. daily for 30 days) significantly reduced the brain protein levels of cyclooxygenase (COX)-1 and **COX-2**, without altering the mRNA levels of these enzymes. COX activity was decreased, as were the brain concentrations of 11-dehydrothromboxane B2 and prostaglandin E2 (PGE2), metabolites of arachidonic acid (AA) produced via COX. In contrast, the brain protein level of 5-lipoxygenase and the concentration of its AA metabolite **leukotriene B4** were unchanged. In view of published evidence that lithium chloride administered chronically to rats, like chronic valproate, reduces AA turnover within brain phospholipids, and that lithium post-transcriptionally down-regulates **COX-2** but not **COX**-1 protein level and enzyme activity, these observations suggest that mood stabilizers generally modulate the release and recycling of AA within brain phospholipids, and the conversion of AA via **COX-2** to PGE2 and related eicosanoids. If targeting this part of the 'AA cascade' accounts for their **therapeutic** action, non-steroidal **anti-inflammatory** drugs or selective **COX-2** inhibitors might prove effective in bipolar disorder.

L83 ANSWER 2 OF 41 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 2
ACCESSION NUMBER: 2002:171113 BIOSIS
DOCUMENT NUMBER: PREV200200171113
TITLE: **Treatment** of **inflammation** and **inflammation**-related disorders with a combination of a **cyclooxygenase-2** inhibitors and a **leukotriene B4** receptor antagonist.
AUTHOR(S): Isakson, Peter C.; Anderson, Gary D.; Gregory, Susan A.
ASSIGNEE: G. D. Searle & Co.
PATENT INFORMATION: US 6342510 January 29, 2002
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Jan. 29, 2002) Vol. 1254, No. 5, pp. No Pagination. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
AB Combinations of a **cyclooxygenase-2** inhibitor and a **leukotriene B4** receptor antagonist are described for **treatment** of **inflammation** and **inflammation**-related disorders.

L83 ANSWER 3 OF 41 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-666669 [71] WPIDS
CROSS REFERENCE: 1997-065309 [06]; 2002-279332 [32]
DOC. NO. CPI: C2002-187040
TITLE: New combination of a **cyclooxygenase-2** inhibitor and a **leukotriene B4** receptor antagonist, useful for **treating inflammatory** disorders, especially arthritis.
DERWENT CLASS: B05

INVENTOR(S): ANDERSON, G D; GREGORY, S A; ISAKSON, P C
PATENT ASSIGNEE(S): (PHAA) PHARMACIA CORP
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2002107276	A1	20020808	(200271)*		20

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2002107276	A1 CIP of	US 1995-489415	19950612
	Cont of	US 1996-661641	19960611
		US 2002-38080	20020103

FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 2002107276	A1 Cont of	US 6342510

PRIORITY APPLN. INFO: US 1996-661641 19960611; US 1995-489415 19950612; US 2002-38080 20020103
AN 2002-666669 [71] WPIDS
CR 1997-065309 [06]; 2002-279332 [32]
AB US2002107276 A UPAB: 20021105
NOVELTY - Combination of a **cyclooxygenase-2** inhibitor (I) and a **leukotriene B4** receptor antagonist (II) is new.
ACTIVITY - **Antiinflammatory**; antiarthritic.
Test details are described but no results given.
MECHANISM OF ACTION - **Cyclooxygenase-2** inhibitor; **leukotriene B4** receptor antagonist.
USE - The combination is useful for **treating inflammatory** disorders, especially arthritis.
Dwg.0/0

L83 ANSWER 4 OF 41 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2003:5634 BIOSIS
DOCUMENT NUMBER: PREV200300005634
TITLE: Adenosine up-regulates cyclooxygenase-2 in human granulocytes: Impact on the balance of eicosanoid generation.
AUTHOR(S): Pouliot, Marc (1); Fiset, Marie-Elaine; Masse, Mireille; Naccache, Paul H.; Borgeat, Pierre
CORPORATE SOURCE: (1) Centre de Recherche en Rhumatologie et Immunologie, Centre Hospitalier de l'Universite Laval, 2705 Laurier Boulevard, Office T1-49, Sainte-Foy, Quebec, G1V 4G2, Canada: Marc.Pouliot@crchul.ulaval.ca Canada
SOURCE: Journal of Immunology, (November 1 2002) Vol. 169, No. 9, pp. 5279-5286. print.
ISSN: 0022-1767.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Polymorphonuclear neutrophils (granulocytes; PMNs) are often the

first blood cells to migrate toward inflammatory lesions to perform host defense functions. PMNs respond to specific stimuli by releasing several factors and generate lipid mediators of inflammation from the 5-lipoxygenase and the inducible **cyclooxygenase** (**COX**)-**2** pathways. In view of adenosine's **anti-inflammatory** properties and suppressive impact on the 5-lipoxygenase pathway, we addressed in this study the impact of this autacoid on the **COX-2** pathway. We observed that adenosine up-regulates the expression of the **COX-2** enzyme and mRNA. Production of PGE2 in response to exogenous arachidonic acid was also increased by adenosine and correlated with **COX-2** protein levels. The potentiating effect of adenosine on **COX-2** could be mimicked by pharmacological increases of intracellular cAMP levels, involving the latter as a putative second messenger for the up-regulation of **COX-2** by adenosine. Specific **COX-2** inhibitors were used to confirm the predominant role of the **COX-2** isoform in the formation of prostanoids by stimulated PMNs. Withdrawal of extracellular adenosine strikingly emphasized the inhibitory potential of PGE2 on **leukotriene B4** formation and involved the EP2 receptor subtype in this process. Thus, adenosine may promote a self-limiting regulatory process through the increase of PGE2 generation, which may result in the inhibition of PMN functions. This study identifies a new aspect of the **anti-inflammatory** properties of adenosine in leukocytes, introducing the concept that this autacoid may exert its immunomodulatory activities in part by modifying the balance of lipid mediators generated by PMNs.

L83 ANSWER 5 OF 41 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2002089299 MEDLINE
DOCUMENT NUMBER: 21659759 PubMed ID: 11714717
TITLE: Ebselen, a glutathione peroxidase mimetic seleno-organic compound, as a multifunctional antioxidant. Implication for inflammation-associated carcinogenesis.
AUTHOR: Nakamura Yoshimasa; Feng Qing; Kumagai Takeshi; Torikai Koji; Ohigashi Hajime; Osawa Toshihiko; Noguchi Noriko; Niki Etsuo; Uchida Koji
CORPORATE SOURCE: Laboratory of Food and Biodynamics, Nagoya University Graduate School of Bioagricultural Sciences, Nagoya 464-8601, Japan.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Jan 25) 277 (4) 2687-94.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20020131
Last Updated on STN: 20030105
Entered Medline: 20020225

AB **Ebselen**, a seleno-organic compound showing glutathione peroxidase-like activity, is one of the promising synthetic antioxidants. In the present study, we investigated the antioxidant activities of **ebselen** using a 12-O-tetradecanoylphorbol-13-

acetate (TPA)-**treated** mouse skin model. Double pretreatments of mouse skin with **ebselen** significantly inhibited TPA-induced formation of thiobarbituric acid-reacting substance, known as an overall oxidative damage biomarker, in mouse epidermis, suggesting that **ebselen** indeed acts as an antioxidant in mouse skin. The antioxidative effect of **ebselen** is attributed to its selective blockade of leukocyte infiltration and activation leading to attenuation of the H(2)O(2) level. In in vitro studies, **ebselen** inhibited TPA-induced superoxide generation in differentiated HL-60 cells and lipopolysaccharide-induced **cyclooxygenase-2** protein expression in RAW 264.7 cells. In addition, we demonstrated for the first time that **ebselen** potentiated phase II enzyme activities, including NAD(P)H:(quinone-acceptor) oxidoreductase1 and glutathione S-transferase in cultured hepatocytes and in mouse skin. These results strongly suggest that **ebselen**, a multifunctional antioxidant, is a potential chemopreventive agent in **inflammation**-associated carcinogenesis.

L83 ANSWER 6 OF 41 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2002635732 MEDLINE
DOCUMENT NUMBER: 22282061 PubMed ID: 12392782
TITLE: Cyclooxygenase and 5-lipoxygenase inhibitors protect against mononuclear phagocyte neurotoxicity.
AUTHOR: Klegeris Andis; McGeer Patrick L
CORPORATE SOURCE: Kinsmen Laboratory of Neurological Research, University of British Columbia, Vancouver, BC, Canada V6T 1Z3.
SOURCE: NEUROBIOLOGY OF AGING, (2002 Sep-Oct) 23 (5) 787-94. Journal code: 8100437. ISSN: 0197-4580.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20021024
Last Updated on STN: 20030111
Entered Medline: 20030110

AB Neuroinflammation and oxidative stress are believed to be contributing factors to neurodegeneration in normal aging, as well as in age-related neurological disorders. Reactive microglia are found in increased numbers in aging brain and are prominently associated with lesions in such age-related degenerative conditions as Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). In vitro, stimulated microglia or microglial-like cells secrete neurotoxic materials and are generators of free radicals through their respiratory burst system. Agents that suppress microglial activation are therefore candidates for neuroprotection. We have developed quantitative in vitro assays for measuring neurotoxicity of microglia or other mononuclear phagocytes. Neuronal like SH-SY5Y cells are cultured in supernatants from activated cells of the human monocytic THP-1 line and their survival is followed. Respiratory burst is directly measured on the activated cells. We tested inhibitors of the cyclooxygenase (COX) or the 5-lipoxygenase (5-LOX) pathways as possible neuroprotective agents. The COX pathway generates **inflammatory** prostaglandins, while the 5-LOX pathway

generates **inflammatory** leukotrienes. We found that inhibitors of both these pathways suppressed neurotoxicity in a dose-dependent fashion. They included the COX-1 inhibitor indomethacin; the **COX-2** inhibitor **NS-398**; the mixed **COX-1/COX-2** inhibitor ibuprofen; the nitric oxide (NO) derivatives of indomethacin, ibuprofen and flurbiprofen; the 5-LOX inhibitor REV 5901; and the 5-LOX activating protein (FLAP) inhibitor **MK-886**. The FLAP inhibitor also reduced respiratory burst activity in a more potent manner than indomethacin. Combinations of COX and 5-LOX inhibitors were more effective than single inhibitors. The data suggest that both COX inhibitors and 5-LOX inhibitors may be neuroprotective in vivo by suppressing toxic actions of microglia/macrophages, and that combinations of the two might have greater **therapeutic** potential than single inhibitors of either class.

L83 ANSWER 7 OF 41 MEDLINE DUPLICATE 5

ACCESSION NUMBER: 2002176008 MEDLINE
DOCUMENT NUMBER: 21905240 PubMed ID: 11908571
TITLE: Synthesis of interleukin 1beta, tumor necrosis factor-alpha, and interstitial collagenase (MMP-1) is eicosanoid dependent in human osteoarthritis synovial membrane explants: interactions with antiinflammatory cytokines.
AUTHOR: He Wendy; Pelletier Jean-Pierre; Martel-Pelletier Johanne; Laufer Stefan; Di Battista John A
CORPORATE SOURCE: Osteoarthritis Research Unit, Hopital Notre-Dame, Centre Hospitalier de l'Universite de Montreal, Quebec, Canada.
SOURCE: JOURNAL OF RHEUMATOLOGY, (2002 Mar) 29 (3) 546-53. Journal code: 7501984. ISSN: 0315-162X.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020324
Last Updated on STN: 20021008
Entered Medline: 20020924

AB OBJECTIVE: To determine the level of **leukotriene B4** (LTB4) synthesized and released by synovium of patients with osteoarthritis (OA), and to study the role of lipoxygenase (LO)/cyclooxygenase (COX) products on proinflammatory cytokine and interstitial collagenase (MMP-1) synthesis. METHODS: Human OA synovial explants were cultured in the presence of lipopolysaccharide (L) and the ionophores ionomycin (I) and thapsigargin (T) (LIT) for 72 h at 37 degrees C, and LTB4 released into the culture medium was measured in the absence or presence of a **COX-2**-specific inhibitor, **NS-398**, or the 5-LO activating protein inhibitor Bay-**x-1005**. Increasing concentrations of LTB4 (10(-9) to 10(-6) M) were incubated with explants for 24 h at 37 degrees C, and interleukin 1beta (IL-1beta) and tumor necrosis factor-alpha (TNF-alpha) in the conditioned medium were quantitated by ELISA. The effect of endogenous eicosanoids on basal and induced levels of IL-1beta, TNF-alpha, and MMP-1 synthesis was examined by incubating

explants in the presence of **NS-398** and Bay-**x-1005**. The effect of **antiinflammatory** cytokines rhIL-4, IL-10, and IL-13 on basal and LTB4 dependent stimulation of IL-1beta/TNF-alpha synthesis was studied under titration conditions. RESULTS: Physiologically relevant concentrations (10(-10) to 10(-9) mol/l) of LTB4 were produced in the presence of LIT. Bay-**x-1005** abrogated LTB4 release, while **NS-398** was without effect. LTB4 stimulated IL-1beta and TNF-alpha synthesis with an EC50 of 190 +/- 35 and 45 +/- 9 nmol/l, respectively. Significant concentrations of IL-1beta and TNF-alpha were released (100-200 and 500-600 pg/ml, respectively). Basal and LIT induced IL-1beta and TNF-alpha production were inhibited by Bay-**x-1005** in a dose dependent manner, while the addition of **NS-398** caused a potent stimulatory effect. The preferential **COX-2** inhibitor also induced MMP-1 synthesis in a manner essentially identical to the proinflammatory cytokines. The **antiinflammatory** cytokine IL-4 blocked LTB4 dependent stimulation of IL-1beta and TNF-alpha synthesis. In contrast, IL-10 markedly stimulated both cytokines when incubated alone or in the presence of LTB4 where the effect was additive. CONCLUSION: Endogenous and locally produced eicosanoids regulate proinflammatory cytokine and MMP-1 synthesis under basal and stimulated conditions in vitro, with leukotrienes and prostaglandins having opposite effects in general. The clinical use of **antiinflammatory** drugs that inhibit eicosanoid synthesis requires an appreciation of their relative capacity to inhibit LO/COX in order to predict their effect on the synthesis of proinflammatory cytokines and matrix metalloproteases. IL-10 stimulated proinflammatory cytokine synthesis in our ex vivo culture system.

L83 ANSWER 8 OF 41 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2002482762 MEDLINE
DOCUMENT NUMBER: 22202546 PubMed ID: 12213119
TITLE: Pharmacodynamics and pharmacokinetics of phenylbutazone in calves.
AUTHOR: Arifah A K; Lees P
CORPORATE SOURCE: The Royal Veterinary College, Hawkshead Campus, North Mymms, Hatfield, Hertfordshire, UK.
SOURCE: JOURNAL OF VETERINARY PHARMACOLOGY AND THERAPEUTICS, (2002 Aug) 25 (4) 299-309.
Journal code: 7910920. ISSN: 0140-7783.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20020925
Last Updated on STN: 20021010
Entered Medline: 20021008

AB Phenylbutazone (PBZ) was administered to six calves intravenously (i.v.) and orally at a dose rate of 4.4 mg/kg in a three-period cross-over study incorporating a placebo **treatment** to establish its pharmacokinetic and pharmacodynamic properties. Extravascular distribution was determined by measuring penetration into tissue chamber fluid in the absence of stimulation (transudate) and after stimulation of chamber tissue with the mild irritant carrageenan (exudate). PBZ pharmacokinetics after i.v. dosage was

characterized by slow clearance (1.29 mL/kg/h), long-terminal half-life (53.4 h), low distribution volume (0.09 L/kg) and low concentrations in plasma of the metabolite oxyphenbutazone (OPBZ), confirming previously published data for adult cattle. After oral dosage bioavailability (F) was 66%. Passage into exudate was slow and limited, and penetration into transudate was even slower and more limited; area under curve values for plasma, exudate and transudate after i.v. dosage were 3604, 1117 and 766 microg h/mL and corresponding values after oral dosage were 2435, 647 and 486 microg h/mL. These concentrations were approximately 15-20 (plasma) and nine (exudate) times greater than those previously reported in horses (receiving the same dose rate of PBZ). In the horse, the lower concentrations had produced marked inhibition of eicosanoid synthesis and suppressed the **inflammatory** response. The higher concentrations in calves were insufficient to inhibit significantly exudate prostaglandin E2 (PGE2), **leukotriene B4** (LTB4) and beta-glucuronidase concentrations and exudate leucocyte numbers, serum thromboxane B2 (TxB2), and bradykinin-induced skin swelling. These differences from the horse might be the result of: (a) the presence in equine biological fluids of higher concentrations than in calves of the active PBZ metabolite, OPBZ; (b) a greater degree of binding of PBZ to plasma protein in calves; (c) species differences in the sensitivity to PBZ of the cyclo-oxygenase (COX) isoenzymes, COX-1 and **COX-2** or; (d) a combination of these factors. To achieve clinical efficacy with single doses of PBZ in calves, higher dosages than 4.4 mg/kg will be probably required.

L83 ANSWER 9 OF 41 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 2002053892 MEDLINE
DOCUMENT NUMBER: 21638188 PubMed ID: 11779581
TITLE: A pyrroloquinazoline derivative with anti-inflammatory and analgesic activity by dual inhibition of cyclo-oxygenase-2 and 5-lipoxygenase.
AUTHOR: Rioja Inmaculada; Terencio M Carmen; Ubeda Amalia; Molina Pedro; Tarraga Alberto; Gonzalez-Tejero Antonia; Alcaraz M Jose
CORPORATE SOURCE: Departamento de Farmacologia, Facultad de Farmacia, Universidad de Valencia. Av. Vicent Andres Estelles s/n, 46100 Burjasot, Valencia, Spain.
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (2002 Jan 11) 434 (3) 177-85.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20020419
Entered Medline: 20020418

AB In a previous study, we reported a new pyrroloquinazoline derivative, 3-(4'-acetoxy-3',5'-dimethoxy)benzylidene-1,2-dihydropyrrolo[2,1-b]quinazoline-9-one (PQ), which inhibited human purified 5-lipoxygenase activity and prostaglandin E2 release in lipopolysaccharide-stimulated RAW 264.7 cells. In the present work, we show that PQ inhibits **cyclo-oxygenase-2** activity in intact cell assays (human monocytes) and

purified enzyme preparations (ovine isoenzymes) without affecting cyclo-oxygenase-1 activity. This behaviour was confirmed in vivo by using the zymosan-injected mouse air pouch model, where PQ caused a marked reduction in cell migration and **leukotriene B4** levels at 4 h, as well as inhibition of prostaglandin E2 levels without affecting **cyclo-oxygenase-2** expression at 24 h after zymosan stimulation. In addition, oral administration of this compound significantly reduced carrageenan-induced mouse paw oedema and phenyl-p-benzoquinone-induced writhings in mice. These results indicate that oral PQ exerts analgesic and **anti-inflammatory** effects, which are related to dual inhibition of **cyclo-oxygenase-2** and 5-lipoxygenase activities.

L83 ANSWER 10 OF 41 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 2002265608 MEDLINE
DOCUMENT NUMBER: 21999966 PubMed ID: 12005204
TITLE: The mechanism of action of the new antiinflammatory compound ML3000: inhibition of 5-LOX and COX-1/2.
AUTHOR: Tries S; Neupert W; Laufer S
CORPORATE SOURCE: Preclinical Development, Merckle GmbH, Blaubeuren, Germany.. susatrie@merckle.de
SOURCE: INFLAMMATION RESEARCH, (2002 Mar) 51 (3) 135-43. Journal code: 9508160. ISSN: 1023-3830.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20020514
Last Updated on STN: 20021214
Entered Medline: 20021126

AB OBJECTIVE: We examined the effects of ML3000 and several non-steroidal **antiinflammatory** drugs (NSAIDs) on the synthesis of products of 5-LOX (LTB4, LTC4) and **COX-1/2** (TXB2, PGE2) in vitro and ex vivo in order to further elucidate the mechanism of action of ML3000. METHODS AND RESULTS: Using a human whole blood assay the effect of ML3000 on the shunt of arachidonic acid to the lipoxygenase pathway when COX is blocked was studied. ML3000 (0.3, 1, 3, 10, 30 microg/ml) and indomethacin (0.3, 1, 3, 10, 30 microg/ml) concentration-dependently inhibited the synthesis of PGE2 (IC50 = 3.9 and 4.5 microM). In contrast to ML3000, indomethacin produced an increase of LTC4 of up to 155.5% of control. 5-lipoxygenase inhibition was further tested in a basophilic leukemia cell assay using RBL-1 cells. ML3000 (1-10 microM) inhibited the synthesis of LTB4 in a concentration related manner (IC50: 3.6 microM). In carrageenan induced rat paw edema, ML3000 and indomethacin completely blocked the formation of PGE2 in the inflamed tissue. The LTB4 production in the inflamed paw was reduced to basal levels by ML3000 (10 +/- 1.4 pg/paw saline control and 7.5 +/- 1.3-5.9 +/- 3.2 pg/paw ML3000), whereas LTB4 levels remained markedly elevated as compared to saline control by indomethacin (30.7 pg/paw). 5-LOX inhibition in the inflamed rat colon was investigated by measuring LTB4 synthesis. **MK-886** and ML3000 at 10 mg/kg p.o. reduced LTB4 production to 29.8 +/- 4.9 and 30.1 +/- 2.8 pg/mg tissue as compared to control (54.2 +/- 7.4 mg/kg tissue). LTB4 levels in the rat stomach were comparable to control (2.5 +/- 0.4 pg/mg protein) after oral

administration of ML3000 (10, 30, 100 mg/kg), whereas oral treatment with indomethacin (0.3, 1, 3 mg/kg) or diclofenac (1, 3 mg/kg) increased LTB4 up to 9.2 +/- 2.3 or 8.9 +/- 1.6 pg/mg protein. This effect was significant at 1 mg/kg diclofenac and 0.3 mg/kg indomethacin. CONCLUSIONS: These results provide further evidence, that ML3000 inhibits 5-LOX as well as COX-1 and **COX-2** in vitro and in animal experiments. The favourable gastrointestinal (GI) tolerability of the compound is believed to be linked to the mechanism of combined 5-LOX and **COX-1/2** inhibition of ML3000.

L83 ANSWER 11 OF 41 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2001-475649 [51] WPIDS
DOC. NO. CPI: C2001-142565
TITLE: Solid composition for delivery of active agents e.g. glyburide comprises carrier optionally containing a substrate having an encapsulation coat containing hydrophilic surfactants e.g. polyoxyethylene alkylethers.
DERWENT CLASS: A96 B05 B07
INVENTOR(S): CHEN, F; PATEL, M V
PATENT ASSIGNEE(S): (LIPO-N) LIPOCINE INC; (CHEN-I) CHEN F; (PATE-I) PATEL M V
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001037808	A1	20010531	(200151)*	EN	106
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW					
US 6248363	B1	20010619	(200151)		
AU 2001017981	A	20010604	(200153)		
EP 1233756	A1	20020828	(200264)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
US 2003064097	A1	20030403	(200325)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2001037808	A1		WO 2000-US32255	20001122
US 6248363	B1		US 1999-447690	19991123
AU 2001017981	A		AU 2001-17981	20001122
EP 1233756	A1		EP 2000-980761	20001122
			WO 2000-US32255	20001122
US 2003064097	A1	Div ex	US 1999-447690	19991123
			US 2001-800593	20010306

FILING DETAILS:

PATENT NO	KIND	PATENT NO

AU 2001017981	A	Based on	WO 200137808
EP 1233756	A1	Based on	WO 200137808
US 2003064097	A1	Div ex	US 6248363

PRIORITY APPLN. INFO: US 1999-447690 19991123; US 2001-800593 20010306

AN 2001-475649 [51] WPIDS

AB WO 200137808 A UPAB: 20021031

NOVELTY - Composition for improved delivery of active agent comprising a solid carrier optionally containing a substrate having an encapsulation coat, where the solid carrier or encapsulation coat contains at least one active agent (I) and one hydrophilic surfactant (II), is new.

ADVANTAGE - The composition is used to deliver a wide variety of active agents having improved absorption and/or biovailability. It provides coated substrate materials without the need for binders. Prior art solid carriers are limited to a few specific drugs due to difficulties in formulating appropriate drug/exicipient compositions to effectively coat the active agent onto a carrier particle. Most of prior art solid dosage forms of hydrophilic active agents exhibit poor or no absorption of the active agent. Non-solid formulations of the same are chemically instable, leak and have capsule shell incompatibility. Conventional solid dosage forms of hydrophobic active agents often exhibit slow and incomplete dissolution and subsequent absorption. They often show a high propensity for biovariability and food interactions of the active agent, resulting in restrictive compliance/labeling requirements. A comparative dissolution study was performed on 3 forms of glyburide (Ia) namely coated beads of (Ia), commercially available (Ia) and pure (Ia) bulk. 5 mg Of each form was usd for triplication dissolution runs in 500 ml of isotonic pH 7.4 phosphate buffer.The dissolutiom medium was sampled at 15, 30, 45, 60, 120 and 180 minutes. The samples were filtered and the filtrates diluted for (Ia)-specific HPLC assay. The (Ia)-coated beads showed a superior dissolution profile in the rate, extent and variability of (Ia) dissolved/released into the medium.

Dwg.0/3

L83 ANSWER 12 OF 41 WPIDS (C) 2003 THOMSON DERWENT

ACCESSION NUMBER: 2001-558457 [63] WPIDS

DOC. NO. CPI: C2001-166257

TITLE: New pyridyl- or pyrimidinyl-substituted bicyclic pyrrole derivatives, are cyclokine release inhibitors useful for treating immune system-related disorders, e.g. cancer, multiple sclerosis or arthritis.

DERWENT CLASS: B02

INVENTOR(S): LAUFER, S; STRIEGEL, H; TOLLMANN, K; TRIES, S; STRIEGEL, H G

PATENT ASSIGNEE(S): (MERC) MERCKLE GMBH CHEM PHARM FAB; (MERC) MERCKLE GMBH

COUNTRY COUNT: 95

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
DE 10004157	A1	20010802	(200163)*		22

WO 2001057042 A2 20010809 (200163) GE
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001030219 A 20010814 (200173)
NO 2002003634 A 20020925 (200277)
EP 1252163 A2 20021030 (200279) GE
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
KR 2003005176 A 20030117 (200334)
CN 1396923 A 20030212 (200335)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
DE 10004157	A1	DE 2000-10004157	20000201
WO 2001057042	A2	WO 2001-EP1011	20010131
AU 2001030219	A	AU 2001-30219	20010131
NO 2002003634	A	WO 2001-EP1011	20010131
		NO 2002-3634	20020731
EP 1252163	A2	EP 2001-902370	20010131
		WO 2001-EP1011	20010131
KR 2003005176	A	KR 2002-709854	20020731
CN 1396923	A	CN 2001-804429	20010131

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001030219	A	Based on	WO 200157042
EP 1252163	A2	Based on	WO 200157042

PRIORITY APPLN. INFO: DE 2000-10004157 20000201
AN 2001-558457 [63] WPIDS
AB DE 10004157 A UPAB: 20011031
NOVELTY - 4-Pyridyl- or 4-pyrimidinyl-substituted fused bicyclic pyrrole derivatives (I) are new.

DETAILED DESCRIPTION - Fused pyrrole derivatives of formula (I) and their optical isomers, salts and readily physiologically hydrolyzable esters are new:

one of R1-R3 = 4-pyridyl, 2,4-pyrimidyl (sic) or 3-amino-2,4-pyrimidyl (sic) (optionally substituted by 1 or 2 1-4C alkyl or halo); and

a second of R1-R3 = phenyl or thienyl (both optionally substituted by 1 or 2 1-4C alkyl or halo); and

the third of R1-R3 = H, COOH, (1-6C) alkoxycarbonyl, CH2OH or 1-6C alkyl;

R4, R5 = H or 1-6C alkyl;

X = CH2, S or O; and

n = 1 or 2.

(N.B. Formulae given in the disclosure suggest that '2,4-pyrimidyl' should be 4-pyrimidyl and that '3-amino-2,4-pyrimidyl' should be 2-amino-4-pyrimidyl).

ACTIVITY - Immunomodulator; immunosuppressive; cytostatic; neuroprotective; antiarthritic; **antiinflammatory**; antibacterial; respiratory.

MECHANISM OF ACTION - Cytokine release inhibitor; 5-lipoxygenase inhibitor; cyclooxygenase-1 inhibitor; **cyclooxygenase-2** inhibitor.

In particular (I) inhibit the release of **inflammatory** mediators such as tumor necrosis factor- alpha (TNF alpha), interleukin-1 beta (IL-1 beta), **leukotriene B4** (LTB4) and prostaglandin E2 (PGE2). (3-(4-Fluorophenyl)-2-(4-pyridyl)-6,7-dihydro-5H-pyrrolizin-1-yl)-methanol (Ia) had IC50 values of 4.0 micro M and 5.0 micro M respectively for inhibition of Escherichia coli 026:B6 lipopolysaccharide-induced release of TNF alpha and IL-1 beta in human peripheral blood mononuclear cells.

USE - (I) are cytokine release inhibitors and/or immunomodulators, used for **treating** disorders of the immune system (all claimed). Specific disorders to be **treated** include autoimmune disease, cancer, multiple sclerosis, arthritis, **inflammatory** bowel disease, septic shock, adult respiratory distress syndrome and transplantation problems.

Dwg.0/0

L83 ANSWER 13 OF 41 MEDLINE DUPLICATE 9

ACCESSION NUMBER: 2001268718 MEDLINE
DOCUMENT NUMBER: 21264952 PubMed ID: 11067848
TITLE: Cloning, expression, and up-regulation of inducible rat prostaglandin e synthase during lipopolysaccharide-induced pyresis and adjuvant-induced arthritis.
AUTHOR: Mancini J A; Blood K; Guay J; Gordon R; Claveau D; Chan C C; Riendeau D
CORPORATE SOURCE: Departments of Biochemistry and Molecular Biology and Pharmacology, Merck Frosst Centre for Therapeutic Research, Kirkland, Quebec H9R 4P8, Canada.. joseph_mancini@merck.com
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Feb 9) 276 (6) 4469-75.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010625
Last Updated on STN: 20030105
Entered Medline: 20010621

AB We have cloned and expressed the inducible form of prostaglandin (PG) E synthase from rat and characterized its regulation of expression in several tissues after in vivo lipopoylsaccharide (LPS) challenge. The rat PGE synthase is 80% identical to the human enzyme at the amino acid level and catalyzes the conversion of PGH(2) to PGE(2) when overexpressed in Chinese hamster ovary K1 (CHO-K1) cells. PGE synthase activity was measured using [(3)H]PGH(2) as substrate and stannous chloride to terminate the reaction and convert all unreacted unstable PGH(2) to PGF(2alpha) before high pressure liquid chromatography analysis. We assessed the induction of PGE synthase in tissues from Harlan Sprague-Dawley

rats after LPS-induced pyresis in vivo. Rat PGE synthase was up-regulated at the mRNA level in lung, colon, brain, heart, testis, spleen, and seminal vesicles. **Cyclooxygenase** (**COX**)-**2** and interleukin 1beta were also up-regulated in these tissues, although to different extents than PGE synthase. PGE synthase and **COX-2** were also up-regulated to the greatest extent in a rat model of adjuvant-induced arthritis. The RNA induction of PGE synthase in lung and the adjuvant-**treated** paw correlated with a 3.8- and 16-fold induction of protein seen in these tissues by immunoblot analysis. Because PGE synthase is a member of the membrane-associated proteins in eicosanoid and glutathione metabolism (MAPEG) family, of which leukotriene (LT) C(4) synthase and 5-lipoxygenase-activating protein are also members, we tested the effect of LTC(4) and the 5-lipoxygenase-activating protein inhibitor **MK-886** on PGE synthase activity. LTC(4) and **MK-886** were found to inhibit the activity with IC(50) values of 1.2 and 3.2 microm, respectively. The results demonstrate that PGE synthase is up-regulated in vivo after LPS or adjuvant administration and suggest that this is a key enzyme involved in the formation of PGE(**2**) in **COX-2**-mediated **inflammatory** and pyretic responses.

L83 ANSWER 14 OF 41 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 2001166187 MEDLINE
DOCUMENT NUMBER: 21164930 PubMed ID: 11264253
TITLE: Cyclo-oxygenase and lipoxygenase pathways in mast cell dependent-neurogenic inflammation induced by electrical stimulation of the rat saphenous nerve.
AUTHOR: Le Filliatre G; Sayah S; Latournerie V; Renaud J F; Finet M; Hanf R
CORPORATE SOURCE: Service de Pharmacologie, Laboratoire Innothera, 7 - 9 av Francois Vincent Raspail, BP 12, 94111, Arcueil Cedex, France.. gael.le.filliatre@innothera.com
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (2001 Apr) 132 (7) 1581-9.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010521
Last Updated on STN: 20010521
Entered Medline: 20010517

AB 1. We investigated the role of arachidonic acid metabolism and assessed the participation of mast cells and leukocytes in neurogenic **inflammation** in rat paw skin. We compared the effect of lipoxygenase (LOX) and cyclo-oxygenase (COX) inhibitors on oedema induced by saphenous nerve stimulation, substance P (SP), and compound 48/80. 2. Intravenous (i.v.) pre-**treatment** with a dual COX/LOX inhibitor (RWJ 63556), a dual LOX inhibitor/cysteinyl-leukotriene (CysLt) receptor antagonist (Rev 5901), a LOX inhibitor (AA 861), a five-lipoxygenase activating factor (FLAP) inhibitor (**MK 886**), or a glutathione S-transferase inhibitor (ethacrynic acid) significantly inhibited (40 to 60%) the development of neurogenic oedema, but did not affect cutaneous blood flow. Intradermal (i.d.) injection of

LOX inhibitors reduced SP-induced oedema (up to 50% for RWJ 63556 and **MK 886**), whereas ethacrynic acid had a potentiating effect. 3. Indomethacin and rofecoxib, a highly selective **COX-2** inhibitor, did not affect neurogenic and SP-induced oedema. Surprisingly, the structurally related **COX-2** inhibitors, **NS 398** and nimesulide, significantly reduced both neurogenic and SP-induced oedema (70% and 42% for neurogenic oedema, respectively; 49% and 46% for SP-induced oedema, respectively). 4. **COX-2** mRNA was undetectable in saphenous nerves and paw skin biopsy samples, before and after saphenous nerve stimulation. 5. A mast cell stabilizer, cromolyn, and a H(1) receptor antagonist, mepyramine, significantly inhibited neurogenic (51% and 43%, respectively) and SP-induced oedema (67% and 63%, respectively). 6. The co-injection of LOX inhibitors and compound 48/80 did not alter the effects of compound 48/80. Conversely, ethacrynic acid had a significant potentiating effect. The pharmacological profile of the effect of COX inhibitors on compound 48/80-induced oedema was similar to that of neurogenic and SP-induced oedema. 7. The polysaccharide, fucoidan (an inhibitor of leukocyte rolling) did not affect neurogenic or SP-induced oedema. 8. Thus, (i) SP-induced leukotriene synthesis is involved in the development of neurogenic oedema in rat paw skin; (ii) this leukotriene-mediated plasma extravasation might be independent of mast cell activation and/or of the adhesion of leukocytes to the endothelium; (iii) COX did not appear to play a significant role in this process.

L83 ANSWER 15 OF 41 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:8584 BIOSIS
DOCUMENT NUMBER: PREV200200008584
TITLE: Identification of dual cyclooxygenase-eicosanoid oxidoreductase inhibitors: NSAIDs that inhibit PG-LX reductase/LTB4 dehydrogenase.
AUTHOR(S): Clish, Clary B.; Sun, Yee-Ping; Serhan, Charles N. (1)
CORPORATE SOURCE: (1) Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, MA, 02115: cnserhan@zeus.bwh.harvard.edu USA
SOURCE: Biochemical and Biophysical Research Communications, (November 9, 2001) Vol. 288, No. 4, pp. 868-874. print.
ISSN: 0006-291X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Eicosanoids play key roles in many physiologic and disease processes, and their regulation by nonsteroidal **anti-inflammatory** drugs (NSAIDs) is critical to many **therapeutic** approaches. These autacoids are rapidly inactivated by specific enzymes such as 15-hydroxyprostaglandin dehydrogenase (15-PGDH) and 15-oxoprostaglandin 13-reductase/ **leukotriene B4** 12-hydroxydehydrogenase (PGR/LTB4DH) that act on main series of eicosanoids (i.e., leukotrienes, prostaglandins), and recently found to act in lipoxin inactivation. Here, a panel of NSAIDs was assessed to determine each compound's ability to inhibit eicosanoid-directed activities of

either the recombinant 15-PGDH or the PG-LXR/LTB4DH. The recombinant 15-PGDH that acts on both prostaglandin E2 (PGE2) and lipoxin A4 (LXA4) was not significantly inhibited by the NSAIDs tested. In contrast, several of the widely used NSAIDs were potent inhibitors of the PG-LXR/LTB4DH that metabolizes 15-oxo-PGE2, and LTB4 as well as 15-oxo-LXA4. Diclofenac and indomethacin each inhibited PG-LXR/LTB4DH-catalyzed conversion of 15-oxo-PGE2 to 13,14-dihydro-15-oxo-PGE2 by 70 and 95%, respectively. Also, a **COX-2** inhibitor, niflumic acid, inhibited the PG-LXR/LTB4DH eicosanoid oxidoreductase (EOR) by 80% while other **COX-2** inhibitors such as nimesulide and **NS -398** did not inhibit this enzyme. These results indicate that certain clinically useful NSAIDs such as diclofenac and indomethacin, in addition to inhibiting **cyclooxygenases** (1 and **2**), also interfere with eicosanoid degradation by blocking PG-LXR/LTB4DH (EOR) and are members of a new class of dual cyclooxygenase (COX)-EOR inhibitors. Moreover, they suggest that the impact of NSAIDs on PG-LXR/LTB4DH activities as targets in the local tissue regulation of eicosanoid-mediated processes should be taken into account.

L83 ANSWER 16 OF 41 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 2002060223 MEDLINE
DOCUMENT NUMBER: 21643058 PubMed ID: 11785783
TITLE: Anti-inflammatory activity of a novel selective cyclooxygenase-2 inhibitor, FR140423, on type II collagen-induced arthritis in Lewis rats.
AUTHOR: Ochi T; Goto T
CORPORATE SOURCE: Department of Immunology and Inflammation, Medicinal Biology Research Laboratories, Fujisawa Pharmaceutical Co, Ltd, Osaka, Japan.. takehiro_ochi@po.fujisawa.co.jp
SOURCE: PROSTAGLANDINS AND OTHER LIPID MEDIATORS, (2001 Dec) 66 (4) 317-27.
Journal code: 9808648. ISSN: 1098-8823.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20020628
Entered Medline: 20020627

AB The mechanism of action of FR140423 (3-(difluoromethyl)-1-(4-methoxyphenyl)-5-[4-(methylsulfinyl)-phenyl]pyrazole), a novel and selective **cyclooxygenase (COX)-2** inhibitor, in rat type II collagen-induced arthritis was investigated and compared with that of indomethacin. We tested the inhibitory effects of FR140423 on paw edema and the formation of arachidonic acid metabolites in inflamed paws immunized with type II collagen. Oral administration of FR 140423 showed a dose-dependent **anti-inflammatory** effect and was two-fold more potent than indomethacin. The increase of prostaglandin (PG) E2 and thromboxane (TX) B2 but not **leukotriene B4** in inflamed paws was associated with the development of paw edema. FR140423 and indomethacin dose-dependently suppressed the levels of PGE2 and TXB2 in arthritic rat paws. Unlike indomethacin, FR140423 did not induce gastric lesions in arthritic rats. These results

suggest that FR140423 shows a potent **anti-inflammatory** effect mediated by inhibition of prostanoids produced by **COX-2** in inflamed tissues immunized with type II collagen, with a greatly improved safety profile compared to indomethacin.

L83 ANSWER 17 OF 41 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 2001250348 MEDLINE
DOCUMENT NUMBER: 21243591 PubMed ID: 11346221
TITLE: Endoscopic comparison of the gastroduodenal safety and the effects on arachidonic acid products between meloxicam and piroxicam in the treatment of osteoarthritis.
AUTHOR: Chang D M; Young T H; Hsu C T; Kuo S Y; Hsieh T C
CORPORATE SOURCE: Division of Rheumatology/Immunology/Allergy, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC.
SOURCE: CLINICAL RHEUMATOLOGY, (2001) 20 (2) 104-13. Journal code: 8211469. ISSN: 0770-3198.
PUB. COUNTRY: Belgium
DOCUMENT TYPE: (CLINICAL TRIAL) Journal; Article; (JOURNAL ARTICLE) (RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20011001 Last Updated on STN: 20011001 Entered Medline: 20010927

AB Our objective was to evaluate the efficacy, the gastroduodenal safety, and the effects on arachidonic acid products of **meloxicam**, a new acidic enolic non-steroidal **anti-inflammatory** drug which preferentially inhibits **cyclo-oxygenase-2** over **cyclo-oxygenase**-1, versus piroxicam in patients with osteoarthritis of the knee. **Meloxicam** 7.5 mg or piroxicam 20 mg daily was administered for 4 weeks in this double-blind parallel-groups randomised study. The efficacy for pain relief of the two tested medications was assessed by means of visual analogue scale and other clinical parameters. Pre- and post-**treatment** endoscopies were performed, and the findings were scored and recorded. The gastric fluid was aspirated at each time and prostaglandin E2, thromboxane B2 and **leukotriene B4** were determined by ELISA. There was no significant difference between the groups regarding the primary efficacy. Changes in endoscopic findings by means of Lanza score showed statistically significant differences between the two **treatment** groups in favour of **meloxicam** at all sites--gastric, duodenal and total. Within-group comparisons showed a statistically significant difference (worsening) in gastric and total score with piroxicam, but no significant difference with **meloxicam**. The frequency of clinically relevant cases (total score >2) also showed a statistically significant worsening in the piroxicam group. The better GI tolerability of **meloxicam** was also suggested by fewer adverse GI events and no withdrawals due to adverse events compared with piroxicam. The pre-/post-study gastric juice concentration of PGE2, TXB2, and LTB4 in the **meloxicam** group was 135.2 +/- 85.8/71.2 +/- 32.2,

116.3 +/- 81.7/99.4 +/- 107.5 and 388 +/- 321/223 +/- 98 pg/ml respectively. The pre-/post-study gastric juice concentration of PGE2, TXB2 and LTB4 in the piroxicam group was 105.7 +/- 43.1/68.2 +/- 34.9, 94.0 +/- 50.9/105.9 +/- 121.1 and 625 +/- 1574/828 +/- 1464 pg/ml, respectively. Both **meloxicam** and piroxicam significantly inhibited gastric PGE2 levels after 4 weeks' **treatment**; however, there was no difference between these two groups. Neither of these medications had an effect on TXB2. Only **meloxicam** inhibited LTB4 concentration significantly, and the between-groups difference was significant. **Meloxicam** 7.5 mg once daily had better gastrointestinal tolerability and an efficacy comparable to that of piroxicam 20 mg over 4 weeks in patients with osteoarthritis of the knee.

L83 ANSWER 18 OF 41 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2000-647325 [62] WPIDS
DOC. NO. CPI: C2000-195856
TITLE: New amino- or imino-substituted carboxylic, phosphonic or sulfonic acid derivatives, are orally active leukotriene A4 hydrolase inhibitors useful e.g. as antiinflammatory, hepatoprotective or antimitotic agents.
DERWENT CLASS: B05
INVENTOR(S): CHAIDRON, L; CHAMARD, O; DANVY, D; DUHAMEL, P; GROS, C; MONTEIL, T; NOEL, N; PIETRE, S; PLAQUEVENT, J C; ROUSSEAU, J M; SCHWARTZ, J C; DUHAMEL, L; LECOMTE, J; PIETTRE, S; PLAQUEVENT, J; SCHWARTZ, J
PATENT ASSIGNEE(S): (BIOP-N) BIOPROJET; (INRM) INSERM INST NAT SANTE & RECH MEDICALE; (INRM) INST NAT SANTE & RECH MEDICALE
COUNTRY COUNT: 24
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000059864	A1	20001012	(200062)*	FR	108
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: CA JP KR MX US					
FR 2791982	A1	20001013	(200062)		
EP 1165491	A1	20020102	(200209)	FR	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
KR 2001108437	A	20011207	(200236)		
JP 2003506317	W	20030218	(200315)		119

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000059864	A1	WO 2000-FR876	20000406
FR 2791982	A1	FR 1999-4271	19990406
EP 1165491	A1	EP 2000-917145	20000406
		WO 2000-FR876	20000406
KR 2001108437	A	KR 2001-712548	20010929
JP 2003506317	W	JP 2000-609377	20000406
		WO 2000-FR876	20000406

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1165491	A1	Based on	WO 200059864
JP 2003506317	W	Based on	WO 200059864

PRIORITY APPLN. INFO: FR 1999-4271 19990406
AN 2000-647325 [62] WPIDS
AB WO 200059864 A UPAB: 20011119
NOVELTY - Amino- or imino-substituted carboxylic, phosphonic or sulfonic acid derivatives (I) are new.

DETAILED DESCRIPTION - Amine or imine-substituted carboxylic, phosphonic or sulfonic acid derivatives of formula (I) and their isomers, diastereomers, enantiomers and salts are new.

X = NH2 or -N=CR4R5;

n, p = 0 or 1, but not both 1;

m = 0-10;

Y' = O, CH2, S, NH or OCH2;

R1 = H, alkyl, cycloalkyl, phenyl (optionally substituted by one or more of halo, CF3, alkyl, alkoxy, NH2, NO2, CN, OH, COOH, phenoxy, benzyloxy, SCH3, SCH2CH3 and NHCOR6), naphthyl, anthracenyl, -A2-(CH2)q-A1, pyridyl, thienyl, furyl or a tricyclic group of formula (i);

Z = COOR7, -P(O)(OR8)(OR9), -P(O)(OR8)R10, tetrazol-5-yl, SO3H, SO2NHR11 or CONHSO2R11;

q = 0-4;

A1, A2 = cycloalkyl, phenyl (optionally substituted by one or more of halo, CF3, alkyl and alkoxy), pyridyl, thienyl, furyl, 2-, 3- or 4-piperidyl or cycloalkenyl;

R2, R3 = H, alkyl, (optionally substituted by halo), CF3 or halo;

R4, R5 = H, alkyl or phenyl (optionally substituted by halo, CF3, alkyl, alkoxy or OH);

r = 0-2;

R6 = alkyl;

R7 = H, alkyl or -(CH2)s-Ph';

s = 0-4;

Ph' = phenyl (optionally substituted by one or more of halo, CF3, alkyl, alkoxy and OH);

R8, R9 = H, phenyl, alkyl or acetylthioalkyl;

R10 = alkyl or -(CH2)t-Ph'';

t = 1-6;

Ph'' = phenyl (optionally substituted by one or more of halo, CF3, alkyl and alkoxy);

R11 = 1-alkyl or phenyl; and

provided that: (i) if Z = COOR7, n = p = 0, R2 = H and R1 = optionally substituted phenyl, then m is other than 1; and (ii) the following compounds are excluded: 2-amino-3-phenoxypropionic acid, 3-amino-7-phenylheptanoic acid, 3-amino-6-phenoxyhexanoic acid and 2-amino-5-phenoxypentanoic acid.

INDEPENDENT CLAIMS are included for:

(1) the use of (I) (including the known compounds excluded by provisos (i) and (ii)) for the production of a leukotriene A4 hydrolyse inhibiting medicament; and

(2) a pharmaceutical composition containing as active agents (I) (including the known compounds excluded by provisos (i) and (ii)) and a **cyclooxygenase** inhibitor.

ACTIVITY - **Antiinflammatory**; antiarthritic;

antipsoriatic; hepatotropic; antimitotic.

MECHANISM OF ACTION - Leukotriene A4 (LTA4) hydrolase inhibitor; **leukotriene B4** (LTB4) biosynthesis inhibitor. 2-(RS)-Amino-6-(4-benzylphenoxy)-hexanoic acid hydrobromide (Ia) had Ki 32 nM for inhibition of LYA4 hydrolase.

USE - (I) (including the known compounds excluded by the provisos) are LTA4 hydrolase inhibitors, for use as **antiinflammatory**, antiarthritic, antipsoriatic, hepatoprotective and antimitotic agents and for treating excessive production of LTB4 induced by cyclooxygenase inhibitors (all claimed).

ADVANTAGE - (I) inhibit LTA4 hydrolase and LTB4 biosynthesis at low concentrations in vitro and at low doses (i.e. less than 1 mg/kg, possibly less than 0.1 mg/kg) on oral administration. They have low toxicity, high bioavailability, good action on oral administration and a long duration of action (especially in the case of aminophosphonate compounds, which can totally inhibit LTA4 in rat blood for more than 24 hours when administered at 1-100 mg/kg p.o.). Dwg.0/0

L83 ANSWER 19 OF 41 MEDLINE DUPLICATE 13

ACCESSION NUMBER: 2000496243 MEDLINE
DOCUMENT NUMBER: 20320869 PubMed ID: 10861857
TITLE: Selenoorganic compound, ebselen, inhibits nitric oxide and tumor necrosis factor-alpha production by the modulation of jun-N-terminal kinase and the NF-kappab signaling pathway in rat Kupffer cells.
AUTHOR: Shimohashi N; Nakamuta M; Uchimura K; Sugimoto R; Iwamoto H; Enjoji M; Nawata H
CORPORATE SOURCE: Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.
SOURCE: JOURNAL OF CELLULAR BIOCHEMISTRY, (2000 Jun 12) 78 (4) 595-606.
Journal code: 8205768. ISSN: 0730-2312.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001027
Last Updated on STN: 20001027
Entered Medline: 20001018

AB In response to the bacterial endotoxin, LPS, Kupffer cells are induced to express NO and TNF-alpha. These compounds are involved in hepatic inflammation/injury, especially that associated with endotoxic shock. In this study, we demonstrate that **ebselen** (2-phenyl-1,2-benzisoselenazol-3[2H]one), a selenoorganic compound, blocks LPS-induced NO and TNF-alpha production by cultured rat liver Kupffer cells. LPS can activate both the NF-kappaB signaling pathway and MAPK signal transduction pathways such as JNK and p38 MAPK. We find that **ebselen** inhibits LPS-induced NF-kappaB nuclear translocalization, and also suppresses the LPS-induced phosphorylation of JNK, but not the phosphorylation of p38 MAPK. This inhibition of signal transduction leads to a decrease in the transcription of TNF-alpha and the inducible isoform of NO. Furthermore, **ebselen** inhibits LPS-induced **COX-2** expression, which is responsible for proinflammatory

prostaglandin production, without affecting constitutive COX-1 expression. These data suggest the mechanism by which **ebselen** acts as an **antiinflammatory** agent, and also suggest that **ebselen** may be potent in preventing hepatic injury such as endotoxic shock, in which Kupffer cell activation has been implicated.

L83 ANSWER 20 OF 41 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 2000408809 MEDLINE
DOCUMENT NUMBER: 20374505 PubMed ID: 10913376
TITLE: Cholesterol modulates vascular reactivity to endothelin-1 by stimulating a pro-inflammatory pathway.
AUTHOR: Paris D; Town T; Humphrey J; Yokota K; Mullan M
CORPORATE SOURCE: Roskamp Institute, University of South Florida, 3515 E. Fletcher Avenue, Tampa, Florida, 33613, USA.. dparis@coml.med.usf.edu
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2000 Aug 2) 274 (2) 553-8.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000901
Last Updated on STN: 20000901
Entered Medline: 20000824

AB Hypercholesterolemia (HC) is associated with coronary endothelial dysfunction and increased circulating levels of endothelin-1. We show that pre-**treatment** of intact rat aortic rings with cholesterol synergistically enhances the vasoconstriction induced by endothelin-1 suggesting that elevated levels of cholesterol may predispose to hypertension by modulating the vascular reactivity to endogenous vasoconstrictors. Moreover, we report that SB202190, a selective inhibitor of p38 MAPK, and PD98059 an inhibitor of MEK1/2 are able to abolish the vasoactive properties of cholesterol. **MK-886**, an inhibitor of 5-lipoxygenase is inefficient at blocking the vasoactive properties of cholesterol whereas **NS-398**, a selective inhibitor of **cyclooxygenase-2** (**COX-2**) completely abolishes cholesterol-induced vasoconstriction. In intact rat aortae, cholesterol stimulates prostaglandin E(2) and prostaglandin F(2 alpha) production, an effect that can be completely prevented by inhibiting p38 MAPK, or **COX-2**. In vitro, cholesterol appears to stimulate a similar pro-**inflammatory** pathway in human cerebrovascular smooth muscle cells. Disruption of the MAPK/**COX-2** pathway may represent a valuable **therapy** to block the hypertension associated with HC, as well as the development of atherosclerosis.

L83 ANSWER 21 OF 41 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. DUPLICATE 15
ACCESSION NUMBER: 2000:341109 BIOSIS
DOCUMENT NUMBER: PREV200000341109

TITLE: An anti-inflammatory ditriazine inhibiting leukocyte functions and expression of inducible nitric oxide synthase and cyclo-oxygenase-2.

AUTHOR(S): Rioja, Inmaculada; Ubeda, Amalia; Terencio, M. Carmen; Guillen, Isabel; Riguera, Ricardo; Quintela, Jose M.; Peinador, Carlos; Gonzalez, Liliana M.; Alcaraz, M. Jose (1)

CORPORATE SOURCE: (1) Departamento de Farmacologia, Facultad de Farmacia, Universidad de Valencia, Av. Vicent Andres Estelles s/n, 46100, Burjasot, Valencia Spain

SOURCE: European Journal of Pharmacology, (26 May, 2000) Vol. 397, No. 1, pp. 207-217. print.
ISSN: 0014-2999.

DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB A ditriazine derivative (4,10-dichloropyrido(5,6:4,5)thieno(3,2-d':3,2-d)-1,2,3-ditriazine (DTD)) inhibited neutrophil functions, including degranulation, superoxide generation, and **leukotriene B4** production, without any effect on 5-lipoxygenase activity. This compound reduced nitric oxide (NO) and prostaglandin E2 production in mouse peritoneal macrophages stimulated with lipopolysaccharide, whereas no influence on the activity of inducible NO synthase, **cyclo-oxygenase -2** or **cyclo-oxygenase**-1 was observed. DTD significantly reduced mouse paw oedema induced by carrageenan and also markedly reduced NO and prostaglandin E2 levels in exudates from 24-h zymosan-stimulated mouse air pouch. Western blot analysis showed that DTD reduced the expression of inducible NO synthase and **cyclo-oxygenase-2**. Our results indicate that DTD exerts **anti-inflammatory** effects related to the inhibition of neutrophil functions and of NO and prostaglandin E2 production, which could be due to a decreased expression of inducible NO synthase and **cyclo-oxygenase-2**.

L83 ANSWER 22 OF 41 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. DUPLICATE 16

ACCESSION NUMBER: 2000:109742 BIOSIS
DOCUMENT NUMBER: PREV200000109742

TITLE: Anti-inflammatory activity of macrolide antibiotics.

AUTHOR(S): Ianaro, Angela; Ialenti, Armando; Maffia, Pasquale; Sautebin, Lidia; Rombola, Laura; Carnuccio, Rosa; Iuvone, Teresa; D'Acquisto, Fulvio; Di Rosa, Massimo (1)

CORPORATE SOURCE: (1) Department of Experimental Pharmacology, University of Naples "Federico II", Via D. Montesano, 49, 80131, Naples Italy

SOURCE: Journal of Pharmacology and Experimental Therapeutics, (Jan., 2000) Vol. 292, No. 1, pp. 156-163.
ISSN: 0022-3565.

DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The effect of four macrolide antibiotics (roxithromycin, clarithromycin, erythromycin, and azithromycin) on the generation of some mediators and cytokines involved in the **inflammatory**

process has been studied both in vivo and in vitro. Rat carrageenin pleurisy was used as a model of acute **inflammation**, and the macrolides were administered (10, 20, and 40 mg/kg p.o.) 1 h before the carrageenin challenge. Exudate volume and leukocyte accumulation were both dose-dependently reduced by roxithromycin, clarithromycin and erythromycin in either normal or adrenalectomized animals. Furthermore, in normal rats, prostaglandin (PG)E2, nitrate plus nitrite, and tumor necrosis factor-alpha levels in pleural exudate were significantly reduced by these macrolides. Roxithromycin appeared more effective than erythromycin and clarithromycin, whereas azithromycin only slightly affected the **inflammatory** reaction. None of the macrolides were able to modify **leukotriene B4** exudate levels. In vitro experiments have shown that the four macrolides (5-80 muM) reduced in a concentration-dependent manner the production of 6-keto-PGF1alpha, NO2-, tumor necrosis factor-alpha, interleukin-1beta, and interleukin-6 by lipopolysaccharide-stimulated J774 macrophages. In J774 cells, the inhibition of 6-keto-PGF1alpha and NO2- production by roxithromycin and erythromycin was not dependent on direct inhibition of **cyclooxygenase-2** and inducible nitric oxide synthase activity because it appears to be related to the inhibition of **cyclooxygenase-2** and inducible nitric oxide synthase protein expression. In conclusion, the present study shows that macrolide antibiotics have **anti-inflammatory** activity, which likely depends on their ability to prevent the production of proinflammatory mediators and cytokines, and suggest that these agents, particularly roxithromycin, can exert **therapeutic** effects independently of their antibacterial activity.

L83 ANSWER 23 OF 41 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 2001011281 MEDLINE
DOCUMENT NUMBER: 20334036 PubMed ID: 10877525
TITLE: New anti-inflammatory treatment strategy in Alzheimer's disease.
AUTHOR: Sugaya K; Uz T; Kumar V; Manev H
CORPORATE SOURCE: The Psychiatric Institute, West Side VA Medical Center, Department of Psychiatry, University of Illinois at Chicago, 60612, USA.
CONTRACT NUMBER: R03 AG16474-01 (NIA)
R01 AG15347 (NIA)
SOURCE: JAPANESE JOURNAL OF PHARMACOLOGY, (2000 Feb) 82 (2) 85-94. Ref: 111
Journal code: 2983305R. ISSN: 0021-5198.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001023

AB Numerous reports have indicated that patients suffering from **inflammatory** diseases (e.g., arthritis) who take **anti-inflammatory** medication have a reduced risk

of developing Alzheimer's disease (AD). Thus, the first generation of **anti-inflammatory** cyclooxygenase (COX) inhibitors, such as aspirin and indomethacin, have been tested as potential **therapeutics** in AD. Because the inhibition of COX-1 is also known to cause tissue damage in the gastrointestinal system from the resultant reduced cytoprotection, selective **COX-2** inhibitors are being investigated and tested clinically as potentially better **therapeutics** for AD patients. However, such drugs may also trigger unwanted effects; for example, the **COX-2** inhibitors, which reduce the production of one type of eicosanoids, the prostaglandins, may increase the production of other eicosanoids; i.e., the **leukotriene B4** (LTB4), which is one of the most potent endogenous chemotactic/**inflammatory** factors. LTB4 production is initiated by the enzyme 5-lipoxygenase (5-LOX). The expression of the 5-LOX gene is upregulated during neurodegeneration and with aging. In spite of the fact that 5-LOX and leukotrienes are major players in the **inflammation** cascade, their role in AD pathobiology/**therapy** has not been extensively investigated. We propose that the 5-LOX **inflammatory** cascade may take part in the process of aging-associated neurodegenerative diseases, and we point to the role of 5-LOX in neurodegeneration and discuss its relevance for **anti-inflammatory therapy** of AD.

L83 ANSWER 24 OF 41 MEDLINE DUPLICATE 18
ACCESSION NUMBER: 1999324221 MEDLINE
DOCUMENT NUMBER: 99324221 PubMed ID: 10393980
TITLE: Local and systemic delivery of a stable aspirin-triggered lipoxin prevents neutrophil recruitment in vivo.
AUTHOR: Clish C B; O'Brien J A; Gronert K; Stahl G L; Petasis N A; Serhan C N
CORPORATE SOURCE: Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital and Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA.
CONTRACT NUMBER: DK-50305 (NIDDK)
GM-38765 (NIGMS)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Jul 6) 96 (14) 8247-52.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990910
Last Updated on STN: 19990910
Entered Medline: 19990826

AB Aspirin (ASA) triggers a switch in the biosynthesis of lipid mediators, inhibiting prostanoid production and initiating 15-epi-lipoxin generation through the acetylation of **cyclooxygenase II**. These aspirin-triggered lipoxins (ATL) may mediate some of ASA's beneficial actions and therefore are of interest in the search for novel

antiinflammatories that could manifest fewer unwanted side effects. Here, we report that design modifications to native ATL structure prolong its biostability in vivo. In mouse whole blood, ATL analogs protected at carbon 15 [15(R/S)-methyl-lipoxin A4 (ATLa1)] and the omega end [15-epi-16-(para-fluoro)-phenoxy-LXA4 (ATLa2)] were recoverable to approximately 90 and 100% at 3 hr, respectively, compared with a approximately 40% loss of native lipoxin A4. ATLa2 retains bioactivity and, at levels as low as approximately 24 nmol/mouse, potently inhibited tumor necrosis factor-alpha-induced leukocyte recruitment into the dorsal air pouch. Inhibition was evident by either local intra-air pouch delivery (approximately 77% inhibition) or systemic delivery by intravenous injection (approximately 85% inhibition) and proved more potent than local delivery of ASA. Rank order for inhibiting polymorphonuclear leukocyte infiltration was: ATLa2 (10 micrograms, i.v.) approximately ATLa2 (10 micrograms, local) approximately dexamethasone (10 micrograms, local) >ASA (1.0 mg, local). Applied topically to mouse ear skin, ATLa2 also inhibited polymorphonuclear leukocyte infiltration induced by **leukotriene B4** (approximately 78% inhibition) or phorbol ester (approximately 49% inhibition), which initiates endogenous chemokine production. These results indicate that this fluorinated analog of natural aspirin-triggered lipoxin A4 is bioavailable by either local or systemic delivery routes and is a more potent and precise inhibitor of neutrophil accumulation than is ASA.

L83 ANSWER 25 OF 41 MEDLINE DUPLICATE 19
ACCESSION NUMBER: 1999413014 MEDLINE
DOCUMENT NUMBER: 99413014 PubMed ID: 10483516
TITLE: New insights in the bronchodilatory and anti-inflammatory mechanisms of action of theophylline.
AUTHOR: Juergens U R; Degenhardt V; Stober M; Vetter H
CORPORATE SOURCE: Department of Pulmonary Diseases, Medical Policlinic, University Hospital, Bonn, Germany.
SOURCE: ARZNEIMITTEL-FORSCHUNG, (1999 Aug) 49 (8) 694-8. Journal code: 0372660. ISSN: 0004-4172.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991014
Last Updated on STN: 19991014
Entered Medline: 19991007

AB Phosphodiesterase (PDE) inhibition and adenosine antagonism have been identified as important underlying mechanisms for the bronchodilating and **anti-inflammatory** action of theophylline (CAS 58-55-9). The aim of the present study was to determine the effects of PDE inhibition by theophylline on cAMP and arachidonic acid (AA) metabolism, namely **leukotriene B4** (LTB4) and prostaglandin E2 (PGE2) production, in cultured monocytes in vitro. Monocytes obtained from healthy non-smoking subjects were incubated in adherence at 37 degrees C for 4 h in the presence of theophylline (0.18, 1.8 and 18 micrograms/ml, respectively) and stimulated with LPS (10 micrograms/ml). LTB4, PGE2 and cAMP were measured in the same culture supernatants by

direct enzyme immunoassay. LPS-stimulated generation of cAMP increased significantly (+162%) in the presence of theophylline (18 micrograms/ml); production of LTB4 was suppressed (-42%) compared to the baseline, whereas PGE2 production increased significantly (+39%). Production of cAMP correlated with increased PGE2 production (r = 0.73, p = 0.025) and with suppression of LTB4 (r = 0.67, p = 0.016). These effects were mimicked by cell permeant nucleotides, such as dibutyryl-cAMP but not by dibutyryl-cGMP and could be abolished by ibuprofen. These results provide the first evidence that the clinical efficacy of theophylline may result from inhibition of leukotriene production and its capacity to stimulate PGE2 production. The underlying mechanism is suggested as feedback regulatory induction of **COX-2** by a prostaglandin driven cAMP-mediated process.

L83 ANSWER 26 OF 41 MEDLINE DUPLICATE 20
ACCESSION NUMBER: 2000132598 MEDLINE
DOCUMENT NUMBER: 20132598 PubMed ID: 10669114
TITLE: Eicosanoid release in the endotoxin-primed isolated perfused rat lung and its pharmacological modification.
AUTHOR: Amann R; Schuligoi R; Peskar B A
CORPORATE SOURCE: Department of Experimental and Clinical Pharmacology, University of Graz, Austria.. rainer.amann@kfunigraz.ac.at
SOURCE: INFLAMMATION RESEARCH, (1999 Dec) 48 (12) 632-6. Journal code: 9508160. ISSN: 1023-3830.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000320
Last Updated on STN: 20030401
Entered Medline: 20000306

AB OBJECTIVE: Recent observations have demonstrated a central role of the "inducible" isoform of the **cyclooxygenase** (**COX**), **COX-2**, in the rat lung. Therefore, the reported capacity of selective **COX-2** inhibitors to potentiate the formation of leukotriene (LT) B4 may raise concern about pro-**inflammatory** side effects of such drugs in the respiratory system. The present study was aimed at determining the effects of the **COX-2** inhibitor **NS-398** on the release of COX and 5-lipoxygenase (LOX) metabolites of arachidonic acid in isolated perfused lungs obtained from endotoxin-**treated** rats before and after stimulation with the leukocyte secretagogue N-formyl-methionyl-leucyl-phenylalanine (FMLP). METHODS: Two hours after rats had received endotoxin i.v., the lung was dissected and perfused via the pulmonary artery with physiological salt solution. After an equilibration period of 20 min the outflow was collected (5-min fractions). In the respective **treatment** groups, indomethacin, **NS-398**, or the 5-LOX inhibitor **MK886** were present throughout the experiment, while FMLP was added to the perfusate during a single 5-min period. The concentration of eicosanoids in the outflow was determined by radioimmunoassay. RESULTS: Endotoxin **treatment** of rats resulted in increased expression of **COX-2** mRNA

in lung tissue, and an elevated basal release of the prostaglandin (PG)I2 metabolite 6-keto PGF1alpha, without a detectable increase of leukotriene (LT) formation. In-vitro exposure to FMLP stimulated LT and prostanoid release, which was significantly enhanced in endotoxin-primed lungs, and was suppressed by the 5-LOX inhibitor **MK-886** (3 microM) and the COX-inhibitor indomethacin (5 microM), respectively. Either compound showed selective inhibition of the respective pathway of arachidonic acid metabolism. In endotoxin-primed lungs, the **COX-2** inhibitor **NS-398** (0.3-1.0 microM) depressed basal as well as FMLP-stimulated release of 6-keto PGF1alpha, but did not cause a significant increase of LTB4 or cysteinyl-LT release. CONCLUSIONS: These results suggest that FMLP, presumably acting on **inflammatory** cells trapped in the pulmonary circulation of endotoxin **treated** rats, induced prostanoid formation mainly via the **COX-2** pathway, and that its inhibition by **NS-398** had no detectable potentiating effect on LTB4 or cysteinyl-LT biosynthesis.

L83 ANSWER 27 OF 41 MEDLINE DUPLICATE 21
ACCESSION NUMBER: 1998334053 MEDLINE
DOCUMENT NUMBER: 98334053 PubMed ID: 9670978
TITLE: Inhibition of inducible nitric oxide synthase by peroxisome proliferator-activated receptor agonists: correlation with induction of heme oxygenase 1.
AUTHOR: Colville-Nash P R; Qureshi S S; Willis D; Willoughby D A
CORPORATE SOURCE: Department of Experimental Pathology, St. Bartholomew's and The Royal London School of Medicine and Dentistry, United Kingdom.
SOURCE: JOURNAL OF IMMUNOLOGY, (1998 Jul 15) 161 (2) 978-84. Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199807
ENTRY DATE: Entered STN: 19980811
Last Updated on STN: 19980811
Entered Medline: 19980730

AB Genetic knock-out in mice of peroxisome proliferator-activated receptor-alpha (PPAR alpha) can prolong **inflammation** in response to **leukotriene B4**. Although **cyclooxygenase 2** has been shown to be induced by PPAR activation, the effect of PPAR agonists on the key **inflammatory** enzyme systems of nitric oxide synthase (NOS) and stress proteins has not been investigated. The effect on these of naturally occurring eicosanoid PPAR agonists (**leukotriene B4** and 8(S)-hydroxyeicosatetraenoic acid, which are PPAR alpha selective; PGA2, PGD2, PGJ2, and delta12PGJ2, which are PPAR gamma selective) and the synthetic PPAR alpha agonist Wy14,643 was examined in activated RAW264.7 murine macrophages. **Leukotriene B4** and 8(S)-hydroxyeicosatetraenoic acid stimulated nitrite accumulation, indicative of enhanced NOS activity. PGA2, PGD2, PGJ2, delta12PGJ2, and Wy14,643 reduced nitrite accumulation, with delta12PGJ2 being the most effective. The mechanism behind this reduction was examined using Western blotting. Inhibition of nitrite accumulation was associated with a

fall in inducible NOS protein and an induction of heme oxygenase 1, correlating both dose dependently and temporally. Other proteins examined (**cyclooxygenase 2**, heme oxygenase 2, heat shock protein 70, and glucose-regulated protein 78) were unaffected. The data suggest that naturally occurring PPAR agonists can inhibit the inducible NOS enzyme pathway. This inhibition may be mediated by modulation of the stress protein, heme oxygenase 1. Thus, the generation of eicosanoid breakdown products during **inflammation** may contribute to its eventual resolution by activation of the PPAR system. This system may thus represent a novel target for **therapeutic** intervention in **inflammatory** disease.

L83 ANSWER 28 OF 41 MEDLINE DUPLICATE 22
ACCESSION NUMBER: 1998340207 MEDLINE
DOCUMENT NUMBER: 98340207 PubMed ID: 9675607
TITLE: Measurement of cyclooxygenase inhibition in vivo: a study of two non-steroidal anti-inflammatory drugs in sheep.
AUTHOR: Cheng Z; Nolan A M; McKellar Q A
CORPORATE SOURCE: Department of Veterinary Preclinical Studies, University of Glasgow, UK.
SOURCE: INFLAMMATION, (1998 Aug) 22 (4) 353-66.
Journal code: 7600105. ISSN: 0360-3997.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981021
Last Updated on STN: 19981021
Entered Medline: 19981009

AB The **anti-inflammatory** effects of the non-steroidal **anti-inflammatory** drugs phenylbutazone (PBZ) and flunixin meglumine (FM) and the relationship between the effects and drug concentration in vivo were studied using a subcutaneous tissue-cage model in sheep. Intracaveal injection of carrageenan induced prostaglandin (PG) E2 production in tissue-cage exudate (maximal concentration, 101 nM) with significant increases in white blood cell (WBC) numbers, skin temperature over the inflamed cage and exudate **leukotriene B4** (LTB4) concentration ($P < 0.05$). Intravenous PBZ, 4.4 mg kg-1 produced mild inhibition of exudate PGE2 generation (10%), but greater inhibition of serum TXB2 (75.3%). The IC50 for TXB2 was 36.0 microM. Phenylbutazone did not alter effects on skin temperature, WBC numbers or exudate LTB4 concentrations. Intravenous FM, 1.1 mg kg-1, significantly inhibited carrageenan-induced exudate PGE2 formation (Emax, 100%, IC50, < 0.4 nM) and serum TXB2 generation (Emax, 100%, IC50, 17 nM) for up to 32 h. Flunixin meglumine significantly inhibited the rise in skin temperature but had a limited effect on exudate WBC. Phenylbutazone and FM have distinct effects on carrageenan-induced **cyclooxygenase** (**COX-2**) and platelet **COX** (COX-1). Flunixin meglumine was a more potent COX inhibitor than PBZ and was more selective for the inducible form of COX in vivo.

L83 ANSWER 29 OF 41 MEDLINE DUPLICATE 23

ACCESSION NUMBER: 1998430836 MEDLINE
DOCUMENT NUMBER: 98430836 PubMed ID: 9760036
TITLE: Differential effects of inhibitors of cyclooxygenase (cyclooxygenase 1 and cyclooxygenase 2) in acute inflammation.
AUTHOR: Gilroy D W; Tomlinson A; Willoughby D A
CORPORATE SOURCE: Department of Experimental Pathology, William Harvey Research Institute, Saint Bartholomew's and the Royal London School of Medicine and Dentistry, UK.
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1998 Aug 21) 355 (2-3) 211-7.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20021219
Entered Medline: 19981211

AB The **anti-inflammatory** activity of drugs more selective for cyclooxgenase isoform inhibition (**cyclooxygenase** 1, **cyclooxygenase 2**), were compared in rat carrageenin-induced pleurisy. Suppression of inflammation by **cyclooxygenase 2**-selective inhibitors, **NS-398** (N-[-2-cyclohexyloxy]-4-nitrophenyl methanesulphonamide) and nimesulide (4-nitro-2-phenoxy-methanesulfonanilide), and by piroxicam and aspirin, more selective for cyclooxygenase 1, was measured. Piroxicam and aspirin significantly inhibited inflammatory cell influx, exudate and prostaglandin E2 formation, 6 h after carrageenin injection. **Cyclooxygenase 2** inhibitors had little effect on these parameters with **NS-398** alone reducing prostaglandin E2 levels, but increasing levels of **leukotriene B4**. In contrast, at 3 h after carrageenin injection, **cyclooxygenase 2** inhibitors significantly inhibited all inflammatory parameters however suppression with piroxicam and aspirin was greater, and more pronounced than at 6 h. **NS-398** and nimesulide dosing did not reduce thromboxane B2 production from platelets isolated from rats with carrageenin-induced pleurisy, demonstrating that at the doses used, **cyclooxygenase 2** inhibitors did not inhibit cyclooxygenase 1, as platelets contain only this isoform. Therefore, in the rat carrageenin-induced pleurisy, drugs more selective for the inhibition of cyclooxygenase 1 attenuate inflammation over a wider time frame than **cyclooxygenase 2**-selective drugs, suggesting a significant role for cyclooxygenase 1 in this model. Inhibition of **cyclooxygenase 2** by **NS-398** however, resulted in an increase in the potent chemoattractant **leukotriene B4**.

L83 ANSWER 30 OF 41 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 1998:279286 SCISEARCH
THE GENUINE ARTICLE: ZF149
TITLE: Effect of ebselen on IL-1-induced alterations in cartilage metabolism
AUTHOR: Pratta M A (Reprint); Ackerman N R; Arner E C

CORPORATE SOURCE: DUPONT MERCK PHARMACEUT CO, EXPT STN E400 4237, INFLAMMATORY DIS RES, POB 80400, WILMINGTON, DE 19880 (Reprint); CYGNUS THERAPEUT SYST, REDWOOD CITY, CA 94063
COUNTRY OF AUTHOR: USA
SOURCE: INFLAMMATION RESEARCH, (MAR 1998) Vol. 47, No. 3, pp. 115-121.
Publisher: BIRKHAUSER VERLAG AG, PO BOX 133 KLOSTERBERG 23, CH-4010 BASEL, SWITZERLAND.
ISSN: 1023-3830.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 38
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objective: To evaluate the effect of the antioxidant-like **anti-inflammatory** agent, **ebselen**, on cartilage proteoglycan degradation and to determine whether its cartilage protectant activity is related to its antioxidant activity.

Materials and Methods: Cartilage in organ culture was stimulated with interleukin-1 (IL-1), and proteoglycan degradation was assessed by measuring the amount of sulfated glycosaminoglycan released into the media, proteoglycan synthesis evaluated by [S-35]-sulfate incorporation, and prostaglandin E-2 (PGE(2)) release determined by radioimmunoassay (RIA). Glutathione peroxidase (GSH-Px) activity was evaluated in a coupled test system using NADPH/GSSG reductase as an indicator and cyclooxygenase activity was evaluated using sheep seminal vesicle prostaglandin synthase.

Results: **Ebselen** caused a concentration-dependent inhibition of IL-1-stimulated proteoglycan degradation with an IC50 of 4.7 mu M. Cartilage PGE(2) release was also reduced in the presence of **ebselen** (IC50 = 6.2 mu M). However, at concentrations up to 100 mu M, **ebselen** had no effect on the inhibition of proteoglycan synthesis by IL-1. Induction of proteoglycan breakdown was also inhibited by a sulfur analog of **ebselen**. This analog was devoid of GSH-Px activity and was 50-fold less potent in cyclooxygenase inhibitory activity, but was equipotent to **ebselen** in inhibiting cartilage degradation.

Conclusions: **Ebselen**, unlike other NSAIDs, blocks cartilage proteoglycan breakdown without inhibiting proteoglycan synthesis. This effect is independent of its GSH-Px activity and its ability to inhibit **cyclooxygenase** and PGE(2) production. Therefore, this compound may provide a new mechanism for protecting cartilage matrix from degradative factors in arthritic joints.

L83 ANSWER 31 OF 41 MEDLINE DUPLICATE 24
ACCESSION NUMBER: 1999052312 MEDLINE
DOCUMENT NUMBER: 99052312 PubMed ID: 9836494
TITLE: The role of cyclooxygenase-1 and cyclooxygenase-2 in lipopolysaccharide and interleukin-1 stimulated enterocyte prostanoid formation.
AUTHOR: Longo W E; Damore L J; Mazuski J E; Smith G S; Panesar N; Kaminski D L
CORPORATE SOURCE: Department of Surgery, Theodore Cooper Surgical Research Institute, St Louis University School of Medicine and Health Sciences Center, MO 63110-0250,

USA.
CONTRACT NUMBER: DK-27695 (NIDDK)
SOURCE: MEDIATORS OF INFLAMMATION, (1998) 7 (2) 85-91.
Journal code: 9209001. ISSN: 0962-9351.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990209
Last Updated on STN: 19990209
Entered Medline: 19990125

AB Lipopolysaccharide is an **inflammatory** agent and interleukin-1 is a cytokine. Their pro-**inflammatory** effects may be mediated by prostanoids produced by inducible **cyclooxygenase-2**. The aim of this study was to determine the prostanoids produced by lipopolysaccharide and interleukin-1 stimulated enterocytes through the **cyclooxygenase**-1 and **2** pathways. Cultured enterocytes were stimulated with lipopolysaccharide or interleukin-1beta with and without cyclooxygenase inhibitors. Low concentrations of indomethacin and valerylsalicylic acid (VSA) were evaluated as cyclooxygenase-1 inhibitors and their effects compared with the effects of a specific **cyclooxygenase-2** inhibitor, SC-58125. Prostaglandin E2, 6-keto prostaglandin F1alpha, prostaglandin D2 and **leukotriene B4** levels were determined by radioimmunoassay. Immunoblot analysis using isoform-specific antibodies showed that the inducible **cyclooxygenase** enzyme (**COX-2**) was expressed by 4 h in LPS and IL-1beta **treated** cells while the constitutive COX-1 remained unaltered in its expression. Interleukin-1beta and lipopolysaccharide stimulated the formation of all prostanoids compared with untreated cells, but failed to stimulate **leukotriene B4**. Indomethacin at 20 microM concentration, and VSA inhibited lipopolysaccharide and interleukin 1beta stimulated prostaglandin E2, but not 6-keto prostaglandin F1alpha formation. SC-58125 inhibited lipopolysaccharide and interleukin-1beta stimulated 6-keto prostaglandin F1alpha but not prostaglandin E2 release. The specific **cyclooxygenase-2** inhibitor also inhibited lipopolysaccharide produced prostaglandin D2 but not interleukin-1beta stimulated prostaglandin D2. While SC-58125 inhibited basal 6-keto prostaglandin-F1alpha formation it significantly increased basal prostaglandin E2 and prostaglandin D2 formation. As SC-58125 inhibited lipopolysaccharide and interleukin-1beta induced 6-keto prostaglandin F1alpha production but not prostaglandin E2 production, it suggests that these agents stimulate prostacyclin production through a **cyclooxygenase -2** mediated mechanism and prostaglandin E2 production occurs through a cyclooxygenase-1 mediated mechanism. Prostaglandin D2 production appeared to be variably produced by cyclooxygenase-1 or **cyclooxygenase-2**, depending on the stimulus.

L83 ANSWER 32 OF 41 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1997-424760 [39] WPIDS
DOC. NO. CPI: C1997-135896
TITLE: Suppressing immune, acute or delayed type hypersensitivity response - using leukotriene B.

DERWENT CLASS: B05
INVENTOR(S): ANDERSON, G; GREGORY, S A; ISAKSON, P C
PATENT ASSIGNEE(S): (SEAR) SEARLE & CO G D
COUNTRY COUNT: 76
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9729775	A1	19970821	(199739)*	EN	65
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN YU					
AU 9722500	A	19970902	(199751)		
EP 880362	A1	19981202	(199901)	EN	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE					
JP 2000505445	W	20000509	(200032)		80
US 6172096	B1	20010109	(200104)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9729775	A1		WO 1997-US1422	19970211
AU 9722500	A		AU 1997-22500	19970211
EP 880362	A1		EP 1997-905663	19970211
			WO 1997-US1422	19970211
JP 2000505445	W		JP 1997-529359	19970211
			WO 1997-US1422	19970211
US 6172096	B1	Cont of	US 1996-600580	19960213
			US 1998-75633	19980511

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9722500	A	Based on	WO 9729775
EP 880362	A1	Based on	WO 9729775
JP 2000505445	W	Based on	WO 9729775

PRIORITY APPLN. INFO: US 1996-600580 19960213; US 1998-75633 19980511
AN 1997-424760 [39] WPIDS
AB WO 9729775 A UPAB: 19970926
Suppressing immune, acute or delayed-type hypersensitivity response comprises **treating** a subject with a **leukotriene B4** receptor antagonist and a **cyclooxygenase-2** inhibitor selected from Dupont Dup 697, **Taisho NS-398, meloxicam, flosulide** and compounds of formula (I) or their salts. A = unsaturated or partially unsaturated 5-6 membered heterocyclic or carbocyclic substituent; R1 = heterocyclyl, cycloalkyl, cycloalkenyl or aryl (all optionally substituted by one or more (halo)alkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, (halo)alkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulphinyl, halo or alkylthio); R2 = alkyl or amino; R3 = halo, alkyl, alkenyl,

alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclooxy, alkoxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclo, cycloalkenyl, aralkyl, heterocycloalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulphinyl, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, N-arylaminosulphonyl, arylsulphonyl or N-alkyl-N-arylaminosulphonyl. Also claimed is a combination comprising: (a) a **cyclooxygenase-2** inhibitor; (b) a **leukotriene B4** receptor antagonist and (c) an immunosuppressive drug selected from antiproliferative agents, **antiinflammatory** acting compounds and inhibitors of leukocyte activation.

The leukocyte activation inhibitor is preferably a cyclosporin, especially cyclosporin A. The **leukotriene B4** receptor antagonist is e.g. Bayer Bay-**x-1005** or Ciba-Geigy **CGS-25019C**. The **cyclooxygenase-2** inhibitor is e.g. 3-(3,4-difluorophenyl)-4-(4-methylsulphonylphenyl)-2(5H)-furanone or 4-[5-(3-fluoro-4-methoxyphenyl)-2-(trifluoromethyl)-4-oxazolyl]benzenesulphonamide.

USE - The combination is used in **treatment** of organ rejection, graft versus host disease, systemic lupus erythematosis, multiple sclerosis, aplastic anaemia, insulin dependent diabetes mellitus, rheumatoid arthritis, osteoarthritis, autoimmune diseases, **inflammatory** diseases, allergies, asthma, airway hypersensitivity, septic shock, myesthenia gravis, autoimmune thyroiditis, Grave's disease, autoimmune haemolytic anaemia, autoimmune thrombocytopenia purpura, mixed connective tissue disease, idiopathic Addison's disease, Sjogren's syndrome, urticaria, acute or delayed hypersensitivity responses, Goodpasture's syndrome, contact dermatitis, granuloma, antibody-induced thrombocytopenia, hypersensitivity pneumonitis, glomerulonephritis, thyroiditis, encephalomyelitis, meningitis, skin and muco-epithelial diseases such as psoriasis, lichen, eczema, **inflammatory** bowel disease, Crohn's disease, alopecia areata, pemphigus and pemphigoid, polymyositis, uveitis, Behcet's disease, pulmonary sarcocidiosis, biliary cirrhosis, atopic dermatitis and cancer. The combinations are useful in **treatment** of humans and animals. Dosage of active ingredient is 0.1-2000 (preferably 0.5-500, especially 1-100) mg/kg/day orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

ADVANTAGE - The combination has no side effects.

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L83 ANSWER 33 OF 41 MEDLINE DUPLICATE 25
ACCESSION NUMBER: 97268070 MEDLINE
DOCUMENT NUMBER: 97268070 PubMed ID: 9113364
TITLE: Nitric oxide synthase and cyclo-oxygenase pathways in

the inflammatory response induced by zymosan in the rat air pouch.

AUTHOR: Paya M; Garcia Pastor P; Coloma J; Alcaraz M J
CORPORATE SOURCE: Departamento de Farmacologia, Universidad de Valencia, Facultad de Farmacia, Spain.

SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (1997 Apr) 120 (8) 1445-52.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970709
Last Updated on STN: 19970709
Entered Medline: 19970623

AB 1. We have studied the participation of nitric oxide (NO) in an animal model of **inflammation**, the rat air pouch stimulated with zymosan. 2. Saline or zymosan was injected into 6-day rat air pouches at different time points and measurements were made of cell migration, levels of nitrite/nitrate (NO2/NO3-), prostaglandin E2 (PGE2), **leukotriene B4** (L.TB4) and secretory phospholipase A2 (sPLA2) in exudates. Nitric oxide synthase (NOS) activity was determined in high speed supernatants from cells present in pouch exudates. Western blot analysis was also performed on these samples. 3. Zymosan injection induced a time-dependent increase in leukocyte infiltration, NO2/NO3- levels and cellular NOS activity that reached a peak by 8 h. Western blot analysis showed the same time course for induction of NOS protein. Colchicine administration to rats inhibited cellular infiltration and decreased the levels of NO metabolites and cellular NOS activity zymosan-injected air pouch at 8 h. NOS activity was present in polymorphonuclear leukocytes (PMNs) and monocytes, but not in the lymphocytes present in exudates. This enzyme is calcium-independent and needs NADPH for activity. PGE2 levels in exudates showed a time course inverse to that of NOS activity and NO metabolites, with maximum levels of PGE2 observed at 4 h after zymosan injection. 4. Administration of NG-nitro-L-arginine methyl ester (L-NAME) or aminoguanidine to rats significantly reduced cellular NOS activity, NO2/NO3- levels and chemiluminescence, whereas they were without effect on cell migration and degranulation, eicosanoid levels and sPLA2 activity. 5. **Treatment** of animals with dexamethasone inhibited cellular NOS activity, NO2/NO3- levels, chemiluminescence and the increase in the levels of PGE2 and LTB4, with only a weak effect on elastase release. 6. Administration of the selective **cyclo-oxygenase-2** (**COX-2**) inhibitor **NS398** to rats strongly reduced PGE2 levels in exudates without affecting NO metabolites or NOS activity at 4 h after zymosan injection. 7. Our data indicate that NOS is induced in the zymosan-stimulated rat air pouch model of **inflammation**. This enzyme is expressed in the cells migrating into the air pouch and caused an increased production of NO metabolites in exudates. The results also suggest the presence of an earlier phase in which eicosanoids play the main role, with participation of **COX-2** activity, and a later phase mediated by NO. The endogenous release of NO does not modify prostaglandin biosynthesis in this in vivo model.

L83 ANSWER 34 OF 41 MEDLINE DUPLICATE 26
ACCESSION NUMBER: 97404293 MEDLINE
DOCUMENT NUMBER: 97404293 PubMed ID: 9262379
TITLE: Evaluation of the antiinflammatory activity of a dual cyclooxygenase-2 selective/5-lipoxygenase inhibitor, RWJ 63556, in a canine model of inflammation.
AUTHOR: Kirchner T; Argentieri D C; Barbone A G; Singer M; Steber M; Ansell J; Beers S A; Wachter M P; Wu W; Malloy E; Stewart A; Ritchie D M
CORPORATE SOURCE: The R.W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey 08869, USA.
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1997 Aug) 282 (2) 1094-101. Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19970922
Last Updated on STN: 19970922
Entered Medline: 19970911

AB Sterile perforated polyethylene spheres (wiffle golf balls) were implanted s.c. in beagle dogs. A local **inflammatory** reaction was elicited within the spheres by injecting carrageenan. Changes in leukocyte count, prostaglandin E2, thromboxane B2 and **leukotriene B4** levels were monitored in fluid samples collected over a 24-hr period. Blood samples were also collected at various time points and analyzed for prostaglandin E2 and **leukotriene B4** production after ex vivo calcium ionophore **treatment**. Effects of standard **antiinflammatory** agents (aspirin, indomethacin, dexamethasone, tenidap and zileuton) and newer **cyclooxygenase-2** (**COX-2**) selective agents (nimesulide, nabumetone and SC-58125) were determined after oral administration. Ex vivo inhibition of cyclooxygenase product synthesis (prostaglandin E2, thromboxane B2) in whole blood was used as an indicator of activity for the constitutive COX-1 isoform, although inhibition of the synthesis of these mediators in the chamber exudate during an **inflammatory** process is believed to represent **COX-2** inhibition. **Treatment** effects on **leukotriene B4** production were also determined both ex vivo in whole blood and in the fluid. All of the compounds tested, except aspirin, inhibited leukocyte infiltration into the fluid exudate. Inhibitors that exert their effects on both isozymes of cyclooxygenase attenuate production of cyclooxygenase metabolites in both the **inflammatory** exudate and in peripheral blood ex vivo, although **COX-2** selective inhibitors only demonstrated activity in the exudate. A 5-lipoxygenase inhibitor (zileuton), a corticosteroid (dexamethasone) and a dual **COX-2** selective/5-lipoxygenase inhibitor (RWJ 63556) had similar profiles in that they all inhibited cell infiltration and eicosanoid production in the fluid and also attenuated **leukotriene B4** production in both the fluid and blood.

L83 ANSWER 35 OF 41 EMBASE

ACCESSION NUMBER: 97206333 EMBASE
DOCUMENT NUMBER: 1997206333
TITLE: Combination of a cyclooxygenase-2 inhibitor with a leukotriene B.
AUTHOR: Searle G.D.
CORPORATE SOURCE: . pn29@student.open.ac.uk
SOURCE: Expert Opinion on Therapeutic Patents, (1997) 7/7 (765-766).
Refs: 12
ISSN: 1354-3776 CODEN: EOTPEG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 030 Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB This patent describes administration of several fixed combination of a selective **cyclooxygenase-2** inhibitor with a **leukotriene B4** receptor antagonist for the **treatment** of **inflammatory** diseases.

L83 ANSWER 36 OF 41 MEDLINE DUPLICATE 27
ACCESSION NUMBER: 97366718 MEDLINE
DOCUMENT NUMBER: 97366718 PubMed ID: 9223548
TITLE: Variabilin: a dual inhibitor of human secretory and cytosolic phospholipase A2 with anti-inflammatory activity.
AUTHOR: Escrig V; Ubeda A; Ferrandiz M L; Darias J; Sanchez J M; Alcaraz M J; Paya M
CORPORATE SOURCE: Department of Pharmacology, University of Valencia and Institute of Natural Products and Agrobiology, Tenerife, Spain.
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1997 Jul) 282 (1) 123-31.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970813
Last Updated on STN: 19970813
Entered Medline: 19970807

AB The marine product variabilin was identified as a novel inhibitor of phospholipase A2 (PLA2), which exhibited IC50 values of 6.9 microM and 7.9 microM for human synovial secretory PLA2 and U937 cells cytosolic PLA2 activities, respectively. This compound was less potent on bee venom or zymosan-injected rat air pouch enzymes and failed to affect Naja naja venom PLA2. The production of **leukotriene B4** by human neutrophils stimulated with calcium ionophore A23187 was also inhibited by variabilin, which was without effect on 5-lipoxygenase, cyclo-oxygenase 1 and **cyclo-oxygenase 2** activities in cell-free assays. Other functions of human neutrophils, such as degranulation and superoxide generation, were also significantly reduced in vitro. Variabilin administered topically suppressed the mouse ear edema induced by 12-O-tetradecanoylphorbol 13-acetate,

whereas the ear edema induced by arachidonic acid was unaffected; this suggests an action previous to arachidonic acid metabolism. This compound administered p.o. at 30 mg/kg and 45 mg/kg significantly inhibited mouse paw edema induced by carrageenan and, at 0.01 to 1.0 micromol/pouch in the mouse air pouch injected with zymosan, exerted a marked inhibition on PGE2 and **leukotriene B4** levels in exudates (ID50 values of approximately 0.028-0.029 micromol/pouch), without affecting cell migration. Our results indicate that variabilin is an inhibitor of human secretory and cytosolic PLA2 activities that controls eicosanoid production in vitro and in vivo, inhibits neutrophil degranulation and superoxide generation in vitro and shows **anti-inflammatory** activity after topical or p.o. administration to mice.

L83 ANSWER 37 OF 41 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1997-065309 [06] WPIDS
CROSS REFERENCE: 2002-279332 [32]; 2002-666669 [71]
DOC. NO. CPI: C1997-021497
TITLE: Combinations comprising a **cyclo oxygenase-2** inhibitor and **leukotriene B4** receptor antagonist - are useful in **treatment** of **inflammation** and related disorders.
DERWENT CLASS: B05
INVENTOR(S): ANDERSON, G D; GREGORY, S A; ISAKSON, P C
PATENT ASSIGNEE(S): (SEAR) SEARLE & CO G D
COUNTRY COUNT: 71
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9641645	A1	19961227	(199706)*	EN	73
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG					
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN					
AU 9662694	A	19970109	(199717)		
EP 833664	A1	19980408	(199818)	EN	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE					
JP 11507669	W	19990706	(199937)		88

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9641645	A1	WO 1996-US9905	19960611
AU 9662694	A	AU 1996-62694	19960611
EP 833664	A1	EP 1996-921477	19960611
		WO 1996-US9905	19960611
JP 11507669	W	WO 1996-US9905	19960611
		JP 1997-503237	19960611

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9662694	A	Based on	WO 9641645

EP 833664 A1 Based on WO 9641645
JP 11507669 W Based on WO 9641645

PRIORITY APPLN. INFO: US 1995-489415 19950612
AN 1997-065309 [06] WPIDS
CR 2002-279332 [32]; 2002-666669 [71]
AB WO 9641645 A UPAB: 20021108
Combination comprising: (a) a **cyclooxygenase-2** inhibitor and; and (b) a **leukotriene B4** receptor antagonist is new.
USE- The combinations are useful in **treatment** of **inflammation** and related disorders, e.g. pain, fever, arthritis, asthma, bronchitis, menstrual cramps, tendinitis, bursitis, psoriasis, eczema, burns, dermatitis, **inflammatory** bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, colorectal cancer, migraine headaches, thyroiditis, aplastic anaemia, Hodgkin's disease, scleroderma, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, gingivitis, myocardial ischaemia, retinitis, conjunctivitis, uveitis, cystic fibrosis, Alzheimer's disease, respiratory distress syndrome, atherosclerosis, endotoxin shock syndrome and central nervous system damage resulting from stroke, ischaemia and trauma. They are useful in **treatment** of humans and animals. Admin. of the cpds. is, e.g., oral, topical or parenteral.
ADVANTAGE- No further details.
Dwg.0/0

L83 ANSWER 38 OF 41 MEDLINE DUPLICATE 28
ACCESSION NUMBER: 97008138 MEDLINE
DOCUMENT NUMBER: 97008138 PubMed ID: 8855314
TITLE: Leukocyte lipid body formation and eicosanoid generation: cyclooxygenase-independent inhibition by aspirin.
AUTHOR: Bozza P T; Payne J L; Morham S G; Langenbach R; Smithies O; Weller P F
CORPORATE SOURCE: Harvard Thorndike Laboratory, Beth Israel Hospital, Harvard Medical School, Boston, MA 02215-5491, USA.
CONTRACT NUMBER: AI 22571 (NIAID)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 Oct 1) 93 (20) 11091-6.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19961219
Entered Medline: 19961125
AB Lipid bodies, cytoplasmic inclusions that develop in cells associated with inflammation, are inducible structures that might participate in generating inflammatory eicosanoids. Cis-unsaturated fatty acids (arachidonic and oleic acids) rapidly induced lipid body formation in leukocytes, and this lipid body induction was inhibited by aspirin and nonsteroidal **antiinflammatory** drugs (NSAIDs). Several findings indicates that the inhibitory effect of

aspirin and NSAIDs on lipid body formation was independent of cyclooxygenase (COX) inhibition. First, the non-COX inhibitor, sodium salicylate, was as potent as aspirin in inhibiting lipid body formation elicited by cis-fatty acids. Second, cis-fatty acid-induced lipid body formation was not impaired in macrophages from COX-1 or **COX-2** genetically deficient mice. Finally, NSAIDs inhibited arachidonic acid-induced lipid body formation likewise in macrophages from wild-type and COX-1- and **COX-2**-deficient mice. An enhanced capacity to generate eicosanoids developed after 1 hr concordantly with cis-fatty acid-induced lipid body formation. Arachidonic and oleic acid-induced lipid body numbers correlated with the enhanced levels of **leukotrienes B4** and C4 and prostaglandin E2 produced after submaximal calcium ionophore stimulation. Aspirin and NSAIDs inhibited both induced lipid body formation and the enhanced capacity for forming leukotrienes as well as prostaglandins. Our studies indicate that lipid body formation is an inducible early response in leukocytes that correlates with enhanced eicosanoid synthesis. Aspirin and NSAIDs, independent of COX inhibition, inhibit cis-fatty acid-induced lipid body formation in leukocytes and in concert inhibit the enhanced synthesis of leukotrienes and prostaglandins.

L83 ANSWER 39 OF 41 MEDLINE DUPLICATE 29
ACCESSION NUMBER: 97046663 MEDLINE
DOCUMENT NUMBER: 97046663 PubMed ID: 8891584
TITLE: Inhibition of inflammatory responses by a series of novel dolabrane derivatives.
AUTHOR: Paya M; Ferrandiz M L; Erradi F; Terencio M C; Kijjoa A; Pinto M M; Alcaraz M J
CORPORATE SOURCE: Departamento de Farmacologia, Universidad de Valencia, Facultad de Farmacia, Spain.
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (1996 Sep 19) 312 (1) 97-105.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970206

AB Four dolabrane derivatives isolated from Endospermum diadenum have been studied for their inhibitory effects on murine models of inflammation and human neutrophil functions in vitro. After topical application, akendo 1, akendo 2 and akendo 3 potently inhibited the mouse ear oedema induced by 12-O-tetradecanoylphorbol acetate (TPA) with a striking effect on myeloperoxidase levels. After oral administration, akendo 2 and akendo 3 inhibited mouse paw oedema induced by carrageenan, with a significant reduction in myeloperoxidase levels. In contrast to indomethacin, they did not modify the prostaglandin E2 content of the inflammed paw. None of the compounds affected superoxide generation by human neutrophils. On the contrary, they inhibited degranulation induced by different stimuli. The most effective compounds were akendo 2 and akendo 3, which also inhibited myeloperoxidase activity. All compounds were weak inhibitors of **leukotriene B4** synthesis and

release by human neutrophils, whereas only akendo 3 decreased 5-lipoxygenase activity. Cyclo-oxygenase-1 from human platelets was inhibited mainly by akendo 2 and akendo 3, although with a low potency. The latter compound also reduced weakly the synthesis of prostaglandin E2 by **cyclo-oxygenase-2**. The **anti-inflammatory** activity of these dolabrane derivatives was not related to arachidonic acid mobilization or metabolism.

L83 ANSWER 40 OF 41 MEDLINE DUPLICATE 30
ACCESSION NUMBER: 96118470 MEDLINE
DOCUMENT NUMBER: 96118470 PubMed ID: 8534265
TITLE: Meloxicam: influence on arachidonic acid metabolism. Part II. In vivo findings.
AUTHOR: Engelhardt G; Bogel R; Schnitzler C; Utzmann R
CORPORATE SOURCE: Department of Pharmacological Research, Dr. Karl Thomae GmbH, Biberach/Riss, Germany.
SOURCE: BIOCHEMICAL PHARMACOLOGY, (1996 Jan 12) 51 (1) 29-38. Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199601
ENTRY DATE: Entered STN: 19960220
Last Updated on STN: 19960220
Entered Medline: 19960130

AB **Meloxicam** is a new nonsteroidal **anti-inflammatory** drug (NSAID) derived from enolic acid. Preclinical studies have indicated that **meloxicam** has potent **anti-inflammatory** activity, together with a good gastrointestinal and renal tolerability profile. This report summarizes studies undertaken to compare **meloxicam** to other NSAIDs in the inhibition of the inducible **cyclooxygenase** (**COX-2**) in inflamed areas (pleurisy of the rat, peritonitis of mice) and their influence on the activity of the constitutive cyclooxygenase (COX-1) in stomach, kidney, brain, and blood. In pleurisy of the rat, **meloxicam** was twice as potent as tenoxicam, 3 times as potent as flurbiprofen, 8 times as potent as diclofenac, and 20 times as potent as tenidap at inhibiting prostaglandin E2 (PGE2) biosynthesis. In the peritonitis model in mice, **meloxicam** was approximately twice as active as piroxicam, and more than 10 times as active as diclofenac in the suppression of PGE biosynthesis. Doses of **meloxicam** sufficient to inhibit PGE2 biosynthesis in the pleural exudate and peritoneal exudate had no influence on **leukotriene-B4** (LTB4) or leukotriene-C4 (LTC4) content. The effect of **meloxicam** on the PGE2 content of rat gastric juice and rat urine was weaker than that of piroxicam or diclofenac. **Meloxicam** was a weaker inhibitor of the increased PGE2 concentration in brain of rats and mice (induced by convulsant doses of pentetrazole) than piroxicam, diclofenac, or indomethacin. **Meloxicam** had a weaker effect on serum thromboxane-B2 (TXB2) concentration in rats than piroxicam or tenoxicam. The in vivo findings confirm the results of in vitro tests, conducted separately, showing that **meloxicam** preferentially inhibits **COX-2** over **COX** -1. **COX-2** is the inducible isoenzyme implicated

in the inflammatory response, whereas COX-1 has cytoprotective effects in the gastric mucosa. Therefore, a preferential selectivity for one isoenzyme over another, as displayed by **meloxicam**, may have implications in the clinical setting in terms of a more favorable risk: benefit profile.

L83 ANSWER 41 OF 41 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:321949 BIOSIS
DOCUMENT NUMBER: PREV199699044305
TITLE: Pharmacology of meloxicam, a new non-steroidal anti-inflammatory drug with an improved safety profile through preferential inhibition of COX-2.
AUTHOR(S): Engelhardt, G.
CORPORATE SOURCE: Dep. Biol. Research, Dr. Karl Thomae GmbH, D-88400 Biberach/Riss Germany
SOURCE: British Journal of Rheumatology, (1996) Vol. 35, No. SUPPL. 1, pp. 4-12.
ISSN: 0263-7103.
DOCUMENT TYPE: General Review
LANGUAGE: English
AB This review focuses on key pharmacological findings with a new NSAID, meloxicam. Unlike established NSAIDs, it preferentially inhibits inducible COX-2 in guinea-pig peritoneal macrophages and human COX-2 in COS cells. Compared with other NSAIDs, meloxicam is the most potent inhibitor of prostaglandin biosynthesis in pleural and peritoneal exudate, but only a weak inhibitor in the gastric tract and kidney. Ulcerogenicity in the rat stomach is weak in relation to anti-inflammatory potency, resulting in a high therapeutic index. Meloxicam's high anti-inflammatory potency combined with good tolerability can be explained by its preferential inhibition of COX-2. In adjuvant arthritis rats, meloxicam inhibits not only paw swelling, but also bone and cartilage destruction and systemic signs of disease. It inhibits leucocyte migration, but has no effect on leucotriene B4 or C4. Meloxicam shows a long-lasting anti-inflammatory and analgesic effect on inflammatory pain and reduces pyrogen-induced fever, but has no central nervous system effects. The pharmacokinetic profile of meloxicam in the rat is similar to that in man. Metabolites are inactive.

(FILE 'MEDLINE' ENTERED AT 16:13:00 ON 11 JUN 2003)

L84	7797	SEA FILE=MEDLINE	ABB=ON	PLU=ON	"CYCLOOXYGENASE INHIBITORS"/CT
L85	4378	SEA FILE=MEDLINE	ABB=ON	PLU=ON	"LEUKOTRIENE B4"/CT
L86	157	SEA FILE=MEDLINE	ABB=ON	PLU=ON	L84 AND L85
L87	23	SEA FILE=MEDLINE	ABB=ON	PLU=ON	L86 AND (THERAPY OR THERAPEUTIC USE)/CT
L88	32605	SEA FILE=MEDLINE	ABB=ON	PLU=ON	INFLAMMATION/CT
L89	3	SEA FILE=MEDLINE	ABB=ON	PLU=ON	L87 AND L88

L84	7797	SEA FILE=MEDLINE	ABB=ON	PLU=ON	"CYCLOOXYGENASE INHIBITORS"/CT
L85	4378	SEA FILE=MEDLINE	ABB=ON	PLU=ON	"LEUKOTRIENE B4"/CT
L86	157	SEA FILE=MEDLINE	ABB=ON	PLU=ON	L84 AND L85
L90	13811	SEA FILE=MEDLINE	ABB=ON	PLU=ON	"ANTI-INFLAMMATORY AGENTS"/CT
L91	7	SEA FILE=MEDLINE	ABB=ON	PLU=ON	L86 AND L90

L92 10 L89 OR L91

L92 ANSWER 1 OF 10 MEDLINE
AN 1999239882 MEDLINE
TI Effect of combination of misoprostol and indomethacin on eicosanoid production in carrageenan-induced air pouch inflammation in rats.
AU Sayar K; Melli M
SO EUROPEAN JOURNAL OF PHARMACOLOGY, (1999 Mar 26) 369 (3) 365-71.
Journal code: 1254354. ISSN: 0014-2999.
AB The effect of single or combined administration of indomethacin and misoprostol on the exudate leukocyte count and thromboxane B2, a stable metabolite of thromboxane A2, and on the leukotriene B4 level, as cyclooxygenase and lipoxygenase metabolites of arachidonic acid, was investigated in acute carrageenan-induced air pouch inflammation in rats. Administration of indomethacin (0.25 to 4 mg/kg) 1 h before carrageenan given by the orogastric route reduced the exudate leukocyte count and thromboxane B2 level whereas it increased the exudate leukotriene B4 level dose dependently. Administration of misoprostol, a synthetic prostaglandin E1 analogue, (12.5 to 100 microg/kg) twice daily for two days before carrageenan given by the orogastric route increased the exudate leukocyte count. Combined misoprostol and indomethacin did not change the effect of indomethacin alone on exudate leukocyte count. Misoprostol, when used alone, decreased exudate thromboxane B2 level significantly. However, misoprostol did not change the exudate leukotriene B4 level, while its combination with indomethacin prevented the indomethacin-induced increase in exudate leukotriene B4 level. In conclusion, although misoprostol can be combined with non-steroidal anti-inflammatory drugs in many chronic inflammatory situations, our results indicate that misoprostol may also be combined with indomethacin in acute inflammation without producing any change on the antiinflammatory efficacy of indomethacin in rats.

L92 ANSWER 2 OF 10 MEDLINE
AN 97404293 MEDLINE
TI Evaluation of the antiinflammatory activity of a dual cyclooxygenase-2 selective/5-lipoxygenase inhibitor, RWJ 63556, in a canine model of inflammation.
AU Kirchner T; Argentieri D C; Barbone A G; Singer M; Steber M; Ansell J; Beers S A; Wachter M P; Wu W; Malloy E; Stewart A; Ritchie D M
SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1997 Aug) 282 (2) 1094-101.
Journal code: 0376362. ISSN: 0022-3565.
AB Sterile perforated polyethylene spheres (wiffle golf balls) were implanted s.c. in beagle dogs. A local inflammatory reaction was elicited within the spheres by injecting carrageenan. Changes in leukocyte count, prostaglandin E2, thromboxane B2 and leukotriene B4 levels were monitored in fluid samples collected over a 24-hr period. Blood samples were also collected at various time points and analyzed for prostaglandin E2 and leukotriene B4 production after ex vivo calcium ionophore treatment. Effects of standard antiinflammatory agents (aspirin, indomethacin, dexamethasone, tenidap and zileuton) and newer cyclooxygenase-2 (COX-2) selective agents (nimesulide, nabumetone and SC-58125) were determined after oral administration. Ex vivo inhibition of cyclooxygenase product

synthesis (prostaglandin E2, thromboxane B2) in whole blood was used as an indicator of activity for the constitutive COX-1 isoform, although inhibition of the synthesis of these mediators in the chamber exudate during an inflammatory process is believed to represent COX-2 inhibition. Treatment effects on leukotriene B4 production were also determined both ex vivo in whole blood and in the fluid. All of the compounds tested, except aspirin, inhibited leukocyte infiltration into the fluid exudate. Inhibitors that exert their effects on both isozymes of cyclooxygenase attenuate production of cyclooxygenase metabolites in both the inflammatory exudate and in peripheral blood ex vivo, although COX-2 selective inhibitors only demonstrated activity in the exudate. A 5-lipoxygenase inhibitor (zileuton), a corticosteroid (dexamethasone) and a dual COX-2 selective/5-lipoxygenase inhibitor (RWJ 63556) had similar profiles in that they all inhibited cell infiltration and eicosanoid production in the fluid and also attenuated leukotriene B4 production in both the fluid and blood.

L92 ANSWER 3 OF 10 MEDLINE
AN 94188534 MEDLINE
TI The pharmacologic effects of 5-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-thiadiazole-2(3H)-thione, choline salt (CI-986), a novel inhibitor of arachidonic acid metabolism in models of inflammation, analgesia and gastric irritation.
AU Schrier D J; Baragi V M; Connor D T; Dyer R D; Jordan J H; Imre K M; Lesch M E; Mullican M D; Okonkwo G C; Conroy M C
SO PROSTAGLANDINS, (1994 Jan) 47 (1) 17-30.
Journal code: 0320271. ISSN: 0090-6980.
AB CI-986 is a potent inhibitor of 5-lipoxygenase and cyclooxygenase pathway product biosynthesis from rat basophilic leukemia (RBL) cells. Because metabolites from these pathways have proinflammatory properties, CI-986 was evaluated in several acute and chronic models of inflammation and hyperalgesia. The compound inhibited swelling in the carrageenan footpad edema, Mycobacterium foot-pad edema and adjuvant arthritis models of inflammation with ID40 values of 1.0, 7.7., and 7.2 mg/kg, respectively. It was roughly equivalent in potency to the standard selective cyclooxygenase inhibitor, naproxen (ID40 = 0.7, 6.3, and 3.8 mg/kg, respectively). CI-986 was also evaluated in the acetic acid induced writhing hyperalgesia assay (ID50 = 0.23 mg/kg) and was approximately equipotent with indomethacin (ID50 = 0.87 mg/kg). Although the effects of CI-986 were similar to those of standard nonsteroidal antiinflammatory drugs (NSAIDs) in the inflammation models, its gastrointestinal profile was unique. CI-986 caused no gastrointestinal irritation at doses up to 200 mg/kg in acute and chronic studies. In contrast, standard NSAIDs caused ulcers at doses of 3.7-37 mg/kg after a single dose. Moreover, CI-986 inhibited the release of LTC4 and PGE2 by gastric mucosa and reduced mucosal and vascular damage induced by oral administration of absolute ethanol to rats. These results indicate that CI-986 is a potent nonulcerogenic antiinflammatory agent with novel pharmacologic properties.

L92 ANSWER 4 OF 10 MEDLINE
AN 90347915 MEDLINE
TI Enzyme inhibitors and receptor antagonists in the arachidonic cascade.
AU Arai Y; Kawamura M
SO NIPPON RINSHO. JAPANESE JOURNAL OF CLINICAL MEDICINE, (1990 Jun) 48

(6) 1120-8.
Journal code: 0420546. ISSN: 0047-1852.

L92 ANSWER 5 OF 10 MEDLINE
AN 88049737 MEDLINE
TI SK&F 86002: a structurally novel anti-inflammatory agent that inhibits lipoxygenase- and cyclooxygenase-mediated metabolism of arachidonic acid.
AU Griswold D E; Marshall P J; Webb E F; Godfrey R; Newton J Jr; DiMartino M J; Sarau H M; Gleason J G; Poste G; Hanna N
SO BIOCHEMICAL PHARMACOLOGY, (1987 Oct 15) 36 (20) 3463-70.
Journal code: 0101032. ISSN: 0006-2952.
AB The effects of SK&F 86002 [5-(4-pyridyl)-6 (4-fluorophenyl)-2,3-dihydroimidazo (2,1-b) thiazole] on the generation of eicosanoids in vitro and on inflammatory responses in vivo are described and compared to other non-steroidal anti-inflammatory drugs. SK&F 86002 inhibited prostaglandin H2 (PGH2) synthase activity (IC50 120 microM) as well as prostanoid production by rat basophilic leukemia (RBL-1) cells (IC50 70 microM) and its sonicate (IC50 100 microM) and human monocytes (IC50 1 microM). In addition, SK&F 86002 inhibited the generation of dihydroxyeicosatetraenoic acid (diHETE) and 5-hydroxyeicosatetraenoic acid (5-HETE) by a high speed supernatant fraction of RBL-1 cells (IC50 10 microM). Cellular production of 5-lipoxygenase products was inhibited by SK&F 86002 as measured by leukotriene B4 (LTB4) generation from human neutrophils (IC50 20 microM), leukotriene C4 (LTC4) generation by human monocytes (IC50 20 microM), and 5-HETE production by RBL-1 cells (IC50 40 microM). The in vivo profile of anti-inflammatory activity of SK&F 86002 supports the dual inhibition of arachidonate metabolism as indicated by its activity in inflammation models that are insensitive to selective cyclooxygenase inhibitors. The responses of arachidonic-acid-induced edema in the mouse ear and rat paw, as well as the cell infiltration induced by carrageenan in the mouse peritoneum and by arachidonic acid in the rat air pouch, were inhibited by SK&F 86002 and phenidone but not by the selective cyclooxygenase inhibitors naproxen and indomethacin.

L92 ANSWER 6 OF 10 MEDLINE
AN 87078357 MEDLINE
TI Arachidonic acid metabolism in inflammation and hypersensitivity reactions: a brief introduction.
AU Malmsten C L
SO CEPHALALGIA, (1986) 6 Suppl 4 13-6.
Journal code: 8200710. ISSN: 0333-1024.

L92 ANSWER 7 OF 10 MEDLINE
AN 86042639 MEDLINE
TI Modes of action of aspirin-like drugs.
AU Abramson S; Korchak H; Ludewig R; Edelson H; Haines K; Levin R I; Herman R; Rider L; Kimmel S; Weissmann G
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1985 Nov) 82 (21) 7227-31.
Journal code: 7505876. ISSN: 0027-8424.
AB Current dogma holds that nonsteroidal anti-inflammatory drugs (NSAIDs) act by inhibition of the synthesis and release of prostaglandins. However, NSAIDs also inhibit the activation of neutrophils, which provoke inflammation by releasing products other than prostaglandins. We now report that NSAIDs (e.g., indomethacin,

piroxicam) inhibit activation of neutrophils by inflammatory stimuli, such as C5-derived peptides and leukotriene B4, even when cyclooxygenase products generated in suspensions of stimulated neutrophils (prostaglandin E and thromboxanes) are present. Sodium salicylate (3 mM) greatly inhibited aggregation of neutrophils but had no effect on aggregation of platelets or production of thromboxane induced by arachidonate. Sodium salicylate and other NSAIDs also inhibit calcium movements (45Ca uptake, changes in fluorescence of chlortetracycline and quin-2). Aspirin, sodium salicylate, indomethacin, and piroxicam also enhanced the poststimulation increase in intracellular cyclic AMP. NSAIDs therefore inhibit early steps in neutrophil activation as reflected by their capacity to inhibit movements of Ca and to enhance intracellular levels of cyclic AMP.

L92 ANSWER 8 OF 10 MEDLINE
AN 85184951 MEDLINE
TI Intolerance to aspirin and the nonsteroidal anti-inflammatory drugs.
AU Housholder G T
SO JOURNAL OF ORAL AND MAXILLOFACIAL SURGERY, (1985 May) 43 (5) 333-7.
Journal code: 8206428. ISSN: 0278-2391.
AB A constant enigma has been the ability of aspirin and other structurally unrelated nonsteroidal anti-inflammatory drugs to induce non-IgE mediated allergic reactions. These reactions range from mild hypersensitivity to fatal anaphylaxis. Recent biochemical and pharmacologic studies involving the oxidative metabolism of arachidonic acid in different cells and tissues have provided insights into how this could conceivably occur. The products of cyclo-oxygenase and lipoxygenase pathways of arachidonic acid metabolism and their interactions may provide an approach, if not the solution, to the problem of aspirin intolerance.

L92 ANSWER 9 OF 10 MEDLINE
AN 85044578 MEDLINE
TI Leukotrienes and prostaglandins in asthma.
AU Bisgaard H
SO ALLERGY, (1984 Aug) 39 (6) 413-20.
Journal code: 7804028. ISSN: 0105-4538.
AB Leukotrienes and prostaglandins possess properties which are central in the asthmatic reaction. They are bronchoconstrictors, they inhibit the mucociliary clearance, increase blood flow and permeability and thereby induce edema formation, and they attract and activate leukocytes. They are formed partly by allergic reactions and partly by a large number of other more non-specific reactions. Finally, the concentration of prostanoids has been found increased in the asthmatic reaction in vivo. The leukotrienes have not been traced in vivo in asthmatic attacks so far, but have been found in vivo in man in a specific type I allergic conjunctival reaction. Much evidence suggests that these mediators are relevant in asthmatic diseases, even though prostaglandin inhibitors have no effect in asthma. There still remains the need to investigate the influence on asthmatic diseases by as yet unavailable leukotriene blocking agents. Even though leukotrienes are judged today to be important mediators in asthma, it does not seem reasonable to expect that a single mediator is responsible for asthmatic diseases. Rather, it seems quite likely that asthma is caused by a complex interplay of a large number of mediators, circulating hormones, nervous mechanisms, receptor abnormalities, intracellular metabolic

defects, etc. Despite this complexity, investigations in recent years have increased the knowledge of the biochemistry and human physiological effects of leukotrienes and prostaglandins which has created an improved understanding of the asthmatic reaction's pathophysiology, contributed a pharmacological rationale for previously used therapy, and stimulated new perspectives for specific pharmacological research.

L92 ANSWER 10 OF 10 MEDLINE
AN 84250069 MEDLINE
TI Arachidonic acid metabolism and inflammation. A brief introduction.
AU Malmsten C
SO SCANDINAVIAN JOURNAL OF RHEUMATOLOGY. SUPPLEMENT, (1984) 53 31-45.
Ref: 92
Journal code: 0400360. ISSN: 0301-3847.

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